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Early Hyperglycemia Predicts Multiple Organ Failure and Mortality but Not Infection

Jason L. Sperry, MD, MPH, Heidi L. Frankel, MD, Sue L. Vanek, RN, Avery B. Nathens, MD, PhD, MPH, Ernest E. Moore, MD, Ronald V. Maier, MD, and Joseph P. Minei, MD

Background: Previous studies attempting to characterize the association between early hyperglycemia (EH) and subsequent outcome have been performed without utilization of a strict glycemic control protocol. We sought to characterize the clinical outcomes associated with EH in a cohort of severely injured trauma patients, when a strict glycemic control protocol was used.

Methods: Data were obtained from a multicenter prospective cohort study evaluating clinical outcomes in blunt injured adults with hemorrhagic shock. Known diabetics and patients with isolated traumatic brain injury were excluded from the analysis. A strict glycemic protocol (target glucose, 80–110 mg/dL) was employed. Cox proportional hazard regression was used to evaluate the effects of EH on multiple organ failure (MOF), nosocomial infection (NI), and mortality, after adjusting for the effects of early death on subsequent infection rates.

Results: Overall mortality, MOF, and NI rates for the entire cohort were 19.6%, 37.5%, and 42.2%, respectively, with a mean Injury Severity Score of 31.6 ± 14. Cox proportional hazard regression confirmed that EH was independently associated with almost a twofold higher mortality rate and a 30% higher incidence of MOF, but was not an independent risk factor for NI, after controlling for all important confounders. There continued to be no independent association between EH and NI, even when stratified by infection type (pneumonia, catheter-related bloodstream infection, or urinary tract infection).

Conclusion: These results suggest that EH is a marker of severe physiologic insult after injury, and that strict glycemic control may reduce or prevent the infectious complications previously shown to be associated with hyperglycemia early after injury.

Key Words: Early hyperglycemia, Strict glycemic control, Multiple organ failure, Nosocomial infection.


Hypoglycemia occurs commonly in critically ill patients and is associated with significant morbidity and mortality in them.1–3 Prospective randomized evidence has demonstrated that strict glycemic control (target glucose, 80–110 mg/dL) reduces infectious outcomes, organ failure, and mortality, particularly in elective surgical critical care patients.4 As a result, it has been proposed that strict glycemic control be incorporated into routine care practices, be measured as an index of the quality of intensive care unit (ICU) care, and is a primary component of the Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock.5,6

The relationship between hyperglycemia and poor outcome is even more pronounced after traumatic injury compared with critically ill patients admitted for other reasons.7 The stress response after acute injury promotes insulin resistance and an overall hyperglycemic state, secondary to the acute effects of corticosteroid, growth hormone, glucagon, and catecholamine release.8–12 The level of hyperglycemia soon after a trauma event is thought to correlate with the severity of injury a patient sustains.13 Laird et al. found that early hyperglycemia (EH), defined by a serum glucose >200 mg/dL in the first 24 hours postinjury, was an independent predictor of infection and mortality, in a retrospective analysis of over 500 patients.14 Interestingly, in this study, glucose cutoff values below 200 mg/dL were not associated with worse outcome.

The previous studies attempting to characterize the association between EH and subsequent outcome have been performed without utilization of a strict glycemic control protocol.7,14–17 The purpose of the current analysis was to characterize the clinical outcomes associated with EH in a cohort of severely injured trauma patients, when a strict glycemic control protocol was used. We hypothesized that EH is only a marker of severe physiologic derangement after injury, and that the poor outcomes associated with EH documented in previous studies would be minimized with strict glycemic control implementation.
PATIENTS AND METHODS

This study was a secondary analysis of data derived from an ongoing multicenter prospective cohort study. The Inflammation and the Host Response to Injury Large Scale Collaborative Program is supported by the National Institute of General Medical Sciences and is designed to characterize the genomic and proteomic response in injured patients at risk for multiple organ failure (MOF) after traumatic injury and hemorrhagic shock. Standard operating procedures (SOPs) were developed and implemented across all institutional centers to minimize variation in postinjury care, including a strict glycemic control protocol (target glucose, 80–110 mg/dL). The main objective of this secondary analysis was to determine whether the presence of hyperglycemia, defined as a serum glucose >200 mg/dL, within the first 24 hours after injury was associated with poor clinical outcome. Endpoints evaluated include the incidence of MOF, nosocomial infection (NI) rates, and in-hospital mortality.

Patients admitted to one of seven institutions, during a 3-year period (November 2003 to September 2006), were included in the analysis. Inclusion criteria included blunt mechanism of injury, presence of prehospital or emergency department systolic hypotension (<90 mm Hg) or an elevated base deficit (≥6 meq/L), blood transfusion requirement within the first 12 hours, and any body region exclusive of the head with an Abbreviated Injury Score 2, allowing exclusion of patients with isolated traumatic brain injury. Patients <16 or >90 years of age, and those with cervical spinal cord injury were excluded from enrollment. For the current analysis, so as not to confound EH as a potential marker of poor outcome, patients with a known history of diabetes were also excluded.

Clinical data were entered and stored in TrialDb, a web-based data collection platform, by trained research nurses. Integrity of the data were maintained through ongoing curation and external data review by an independent chart abstractor. When patients were admitted to the ICU, Multiple Organ Dysfunction Scores for renal, hepatic, cardiovascular, metabolic, hematologic, respiratory, and neurologic systems were determined daily. Maximum daily serum glucose levels (single value per day) and insulin requirements (summed hourly insulin requirements averaged during 24 hours, U/h) were recorded, and all nosocomial infectious complications were similarly documented (infection type, culture specimen source, and bacteriology). The diagnosis of MOF required a maximum Multiple Organ Dysfunction Score >5, whereas diagnosis of NI required specific clinical criteria along with positive culture evidence. All time variables to the respective outcome event were determined from the day of initial injury, whereas the time to the first NI was used in those patients with multiple infections. Diagnosis of a ventilator-associated pneumonia required a quantitative culture threshold of ≥10^7 CFU/mL for bronchoalveolar lavage specimens. Diagnosis of catheter-related blood stream infections (CR-BSIs) required positive peripheral cultures with the identical organism obtained from either a positive semiquantitative culture (>15 CFU per segment), or positive quantitative culture (>10^5 CFU per segment) from a catheter segment specimen. Urinary tract infections (UTIs) required >10^5 organisms per milliliter of urine.

The strict glycemic control protocol employed allowed for the use of aggressive sliding scale insulin or intravenous (i.v.) insulin infusion. Subcutaneous regular insulin could be used during the initial 4 hours, but patients with levels remaining outside the target range (80–110 mg/dL) at that time were then started on an insulin infusion. Infusion administration was titrated to blood glucose levels using a scheduled combination of i.v. bolus insulin and adjustments of the continuous infusion rate. Adjustments were performed every 2 hours, and a rate of 30 U/h was the maximum infusion rate employed. For glucose levels below 60 mg/dL, the infusion was stopped and dextrose was administered with levels rechecked 1 hour subsequently. Hourly glucose measurements for patients whose glucose was difficult to control was at the discretion of the bedside nurse or physician.

Data are summarized as mean ± SD, median [interquartile range], or percentage (%). Student’s t or Mann-Whitney statistical tests were used to compare continuous variables, whereas χ^2 or Fisher’s exact test were used for categorical variables. Kaplan–Meier time-to-event analysis and log-rank comparison was undertaken for each outcome of interest (mortality, MOF, and NI). Separate Cox proportional hazard regression models, with MOF, NI, and mortality as the dependent variables, were then created to determine whether EH was an independent risk factor for these outcomes after adjusting for important confounders. Patients who died or who were discharged from the hospital without a respective outcome event were censored, thus adjusting for the effect of early death on subsequent MOF and NI rates. NI outcome was then further stratified into pneumonia, CR-BSI, and UTI, and a similar regression analysis was performed for each. Covariates included in the final models were determined using a 5% change in estimates approach. Covariates were placed individually into a regression model with the EH variable. Those covariates that changed the odds ratio for EH by greater than 5% were considered important confounders and were kept in the final model. Potential covariates tested for inclusion into the final models included patient age, gender, Injury Severity Score, presenting Glasgow Coma Scale score, hypotension upon arrival (systolic blood pressure <90 mm Hg), presence of comorbidities (history of myocardial infarction, congestive heart failure, chronic obstructive lung disease, cirrhosis, smoking, and alcoholism), resuscitation (blood, crystalloid, vasopressor) requirements and base deficit in the first 12 hours, maximum insulin requirements (first 24 hours, U/h), maximum Abbreviated Injury Score, and requirement of either an exploratory laparotomy or thoracotomy/ sternotomy. Clinically relevant interaction terms were tested and kept in the model if statistically significant (p < 0.05). The
institutional review board of each participating center approved the cohort study, and the institutional review board at the University of Texas Southwestern Medical Center approved this current secondary analysis.

RESULTS

Of the 923 patients enrolled during the study period, 59 had a known history of diabetes whereas 14 had incomplete data and were excluded, resulting in 850 patients constituting the study population. Overall mortality, MOF, and NI rates for the entire cohort analyzed were 19.6%, 37.5%, and 42.2%, respectively. The cohort was significantly injured with a mean Injury Severity Score of 31.6 ± 14, with 47% and 12% of patients requiring exploratory laparotomy or thoracotomy/sternotomy, respectively. Over 39% (n = 348) of patients developed EH within 24 hours after injury, with an average maximum glucose of 203 ± 67 (range, 75–492; Fig. 1).

Comparison groups (EH vs. no EH) were clinically similar in age, gender, and mechanism of injury; however, patients who developed EH were more severely injured, had lower presenting Glasgow Coma Scale scores, had a greater base deficit, were more often hypotensive, had greater resuscitative requirements (crystalloid, blood, and vasopressors) within the first 24 hours postinjury, and more often required operative intervention (laparotomy or thoracotomy). Length of stay was similar between the two groups; however, after adjusting for differences in mortality rates between the two groups, patients with EH had significantly lower ICU-free days, ventilator-free days, and hospital-free days (Table 1).

To assess the adequacy of the glycemic control protocol and verify that differences in outcome between the two groups were not caused by a disparity in insulin administration, the maximum daily glucose values and mean hourly insulin requirements for all patients were analyzed. Average maximum glucose values in the first 24 hours after injury for the two groups, by definition, were significantly different (No EH 160 mg/dL ± 25 mg/dL vs. EH 264 mg/dL ± 59 mg/dL, p < 0.01). The average maximum daily glucose values during the first 3 days after injury was 130 mg/dL ± 24 mg/dL (range, 59–251 mg/dL) for all patients. When average maximum values for No EH versus EH groups during the first 3 days postinjury were compared, despite being statistically different, glucose values were clinically similar (No EH 127 mg/dL ± 21 mg/dL vs. EH 135 mg/dL ± 27 mg/dL, p < 0.01). Figure 2 demonstrates the time course of the glycemic control regimen employed in this study for the two comparison groups. This figure verifies that despite significant mean differences early after injury, by postinjury day 1, glycemic control between the two groups is similar and maintained. Patients with EH also had a significantly higher mean hourly insulin requirement during the first 3 days postinjury compared with those without EH, (3.1 U/h ± 2 U/h vs. 2.5 U/h ± 2 U/h, p = 0.013) whereas patients with EH who ultimately died, similarly, had greater mean hourly insulin requirements compared with those who survived (3.8 U/h ± 3 U/h vs. 2.9 U/h ± 2 U/h, p = 0.022).

EH was associated with significantly higher crude mortality and MOF rates; however, there was no difference in crude NI rates (Table 2). Despite stratification of NI into pneumonia, CR-BSI, or UTI, crude rates remained similar between the two groups. Kaplan–Meier analysis and log-rank comparison revealed a significantly higher rate of mortality and MOF for patients with EH relative to those without EH, with the curves separating early in time after injury (Fig. 3). However, the incidence of NI was no different between the two comparison groups. Cox proportional hazard regression confirmed that EH was independently associated with almost a twofold higher mortality rate and a 30% higher incidence of MOF, but was not an independent risk factor for NI, after controlling for all important confounders (Table 3). There continued to be no independent association between EH and NI even after stratification into pneumonia (heart rate [HR] 1.08, 95% CI 0.8–1.4), CR-BSI (HR 1.4, 95% CI 0.6–3.4), or UTI (HR 1.01, 95% CI 0.7–1.4) infection subtypes.

DISCUSSION

Strict glycemic control has been proven to reduce infectious morbidity and mortality in critically ill patients. However, the significance and management of hyperglycemia soon after injury has been less adequately characterized. We demonstrated in this analysis that EH is an independent risk factor for MOF and subsequent mortality, but was not associated with a higher NI risk overall, or when stratified by infection type. It is not known if the association of EH with MOF and mortality is causal and if even more aggressive attainment of target range glucose values sooner after injury may improve these poor outcomes. However, these results suggest that EH is a marker of severe physiologic
derangement postinjury, with a higher mortality risk attributable to MOF rather than NI.

These results are in contrast to previous studies, where EH has been shown to be associated with a higher mortality and greater infectious complications in patients after injury. Sung et al. showed in a prospective analysis on 1,003 consecutive trauma patients a threefold higher risk of overall infectious complications in patients with EH. Similarly, Yendamuri et al. found that EH was independently associated with a threefold higher risk of pneumonia and UTI. As described previously, the Inflammation and the Host Response to Injury Large Scale Collaborative Program employed multiple SOPs to minimize variation in postinjury care across institutions. These included strict glycemic control, early goal directed resuscitation, venous thromboembolism prophylaxis, low-tidal volume strategy, ventilator-associated pneumonia management, and restrictive transfusion protocols.

### Table 1 Baseline Demographics and Characteristics for Comparison Groups

<table>
<thead>
<tr>
<th>Without EH (n = 502)</th>
<th>EH (n = 348)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40.1 ± 17</td>
<td>40.6 ± 19</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>62.0</td>
<td>69.0</td>
</tr>
<tr>
<td>Mechanism of injury (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVC</td>
<td>73.5</td>
<td>71.3</td>
</tr>
<tr>
<td>Ped struck</td>
<td>13.7</td>
<td>13.2</td>
</tr>
<tr>
<td>Fall</td>
<td>6.6</td>
<td>8.6</td>
</tr>
<tr>
<td>Other</td>
<td>6.2</td>
<td>6.9</td>
</tr>
<tr>
<td>ED GCS</td>
<td>9.2 ± 6</td>
<td>6.9 ± 5</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>29.9 ± 13</td>
<td>33.8 ± 13</td>
</tr>
<tr>
<td>Initial base deficit (meq/L)</td>
<td>9.5 ± 4</td>
<td>12.7 ± 6</td>
</tr>
<tr>
<td>ED hypotension (≤90 mm Hg, %)</td>
<td>63.0</td>
<td>70.8</td>
</tr>
<tr>
<td>12-h transfusion requirement (mL)</td>
<td>2,285 ± 2,679</td>
<td>4,038 ± 4,191</td>
</tr>
<tr>
<td>12-h crystalloid requirement (L)</td>
<td>11.4 ± 6</td>
<td>13.3 ± 8</td>
</tr>
<tr>
<td>Max 24-h insulin requirement (U/h)</td>
<td>0.96 ± 2</td>
<td>1.90 ± 3</td>
</tr>
<tr>
<td>24-h vasopressor requirement (%)</td>
<td>14.1</td>
<td>32.8</td>
</tr>
<tr>
<td>Exploratory laparotomy (%)</td>
<td>4.03</td>
<td>52.9</td>
</tr>
<tr>
<td>Thoracotomy/sternotomy/VATS (%)</td>
<td>8.0</td>
<td>17.8</td>
</tr>
<tr>
<td>LOS (d)</td>
<td>20.6 ± 16</td>
<td>21.6 ± 23</td>
</tr>
<tr>
<td>ICU free days*</td>
<td>18 [0–24]</td>
<td>7 [0–20]</td>
</tr>
<tr>
<td>Vent free days*</td>
<td>22 [9–27]</td>
<td>12 [0–22]</td>
</tr>
<tr>
<td>Hospital free days†</td>
<td>40 [24–48]</td>
<td>25 [0–39]</td>
</tr>
<tr>
<td>History of MI (%)</td>
<td>2.0</td>
<td>2.3</td>
</tr>
<tr>
<td>History COPD (%)</td>
<td>3.6</td>
<td>2.0</td>
</tr>
<tr>
<td>History of CHF (%)</td>
<td>0.2</td>
<td>1.4</td>
</tr>
<tr>
<td>History of alcoholism (%)</td>
<td>15.7</td>
<td>9.5</td>
</tr>
<tr>
<td>History of liver Dx (%)</td>
<td>5.8</td>
<td>1.7</td>
</tr>
<tr>
<td>History of smoking (%)</td>
<td>32.3</td>
<td>24.1</td>
</tr>
</tbody>
</table>

* Reported as median and [interquartile range] relative to 28 d.
† Reported as median and [interquartile range] relative to 60 d.
ED, emergency department; GCS, Glasgow Coma Scale score; VATS, video-assisted thoracoscopy; LOS, length of stay; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; Dx, disease.

### Table 2 Crude Outcome Rates for Comparison Groups

<table>
<thead>
<tr>
<th>Without EH (n = 502)</th>
<th>EH (n = 348)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude mortality (%)</td>
<td>11.8</td>
<td>33.0</td>
</tr>
<tr>
<td>Crude MOF (%)</td>
<td>32.3</td>
<td>49.4</td>
</tr>
<tr>
<td>Crude NI (%)</td>
<td>43.8</td>
<td>45.5</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>28.9</td>
<td>31.0</td>
</tr>
<tr>
<td>CR-BSI (%)</td>
<td>2.8</td>
<td>2.9</td>
</tr>
<tr>
<td>UTI (%)</td>
<td>15.1</td>
<td>15.2</td>
</tr>
</tbody>
</table>

Fig. 2. Average maximum daily glucose values (milligram per deciliter) over time for early hyperglycemic and nonhyperglycemic patients (day 0 = within 24 hours from time of injury, error bars represent SD).
used for all enrolled patients. This diminished risk of NI associated with EH may be in part attributable to these evidenced-based SOPs that were employed. The consistency of our findings across different types of infectious outcomes (pneumonia, CR-BSI, or UTI) suggests an overall reduction in infectious risk. To attribute any change in outcome to a glycemic control regimen requires evidence of attainment and maintenance of target level glucose values. As this study is only a secondary analysis of data derived from a prospective cohort study, we are unable to definitively say what intervention is responsible for our findings. However, the most likely explanation is an adequate glycemic control protocol as verified by our analysis. It may be that in previous studies, which attempted to characterized hyperglycemia soon after injury, EH was closely associated with persistent poor glucose control beyond 24 hours, resulting in a greater incidence of infectious complications.7,14–17 However, in the face of a strict glycemic control protocol, “persistent hyperglycemia” is aggressively managed, and these infectious complications are minimized or may even be prevented.

A significant proportion of the organ failure and mortality differences based on EH status occurred very early postinjury, as evidenced by the early separation of the Kaplan–Meier curves. This is consistent with the hypothesis that EH is a significant marker for the severity of physiologic insult after injury. In this cohort of severely injured trauma patients, it seems that the higher mortality risk associated with EH is attributable to early MOF. Further research is needed to determine if earlier insulin administration before admission to the ICU, beginning in the trauma bay or in the operating theater, is beneficial. It is plausible that more aggressive attainment of glucose values within the target range in the first 24 hours may improve these associated poor outcomes. However, the stress response after acute injury, which promotes the insulin resistance and an overall hyperglycemic state, may make this less likely.2,13,29 It may be that, despite aggressive insulin therapy, target range glucose values will not be obtainable in all patients early after injury.

Previous studies have shown that the outcome differences associated with a strict glycemic control regimen are most strongly correlated with treatment of hyperglycemia itself rather than an insulin treatment effect.30 Our results from this analysis are in agreement, as our mortality and MOF findings are independent of the maximum hourly insulin requirement in the first 24 hours after injury. One would expect that the maximum 24-hour glucose and insulin requirements would be correlated, however, the interaction terms between the two covariates were not significant in any of the models, and accordingly excluded. Similarly, a disparity in insulin administration was unlikely responsible, as those who had EH were given significantly more aggressive insulin treatment relative to those without EH, with similar findings in those who ultimately died with EH compared with those who survived.

This analysis has several potential limitations. First, this study is a secondary analysis of a prospective cohort study looking at the genomic and proteomic response after severe injury and hemorrhagic shock. As with any secondary analysis, data were not recorded to answer the specific hypothesis stated for this study. The available serum glucose data were recorded as single maximum daily glucose values when compared with a more advantageous daily average. It is possible that a single spurious glucose value during the first 24 hours could result in an inaccurate classification of a relatively euglycemic patient. Similarly, measuring the average maximum daily value likely inflates our estimates for adequacy of glycemic control and makes it difficult to quantitate the percent of patients within target glucose range. Patients with known diabetes were excluded from the analysis; however, those with undiagnosed or
EH is a marker of severe physiologic insult after injury, associated with EH after injury. The infectious complications previously shown to be associated mortality. However, these results suggest that a strict glycemic protocol may reduce or prevent complications.

In conclusion, EH is independently associated with almost a twofold higher rate of mortality and a 30% higher rate of MOF; however, EH is not an independent risk factor for NI even when stratified by infection type. Further studies are needed to determine whether more aggressive attainment of target glucose values in the first 24 hours after injury may reduce this organ failure rate and associated mortality. However, these results suggest that EH is a marker of severe physiologic insult after injury, and that a strict glycemic protocol may reduce or prevent the infectious complications previously shown to be associated with EH after injury.

### Table 3 Cox Proportional Hazard Regression Models for Mortality, MOF, and NI

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early hyperglycemia (Y/N)</td>
<td>0.003</td>
<td>1.93</td>
<td>1.25–2.94</td>
</tr>
<tr>
<td>12-h blood Tx requirement (≥6 vs. &lt;6 U)</td>
<td>0.016</td>
<td>1.68</td>
<td>1.10–2.57</td>
</tr>
<tr>
<td>ISS (25–41)*</td>
<td>0.211</td>
<td>1.45</td>
<td>0.81–2.61</td>
</tr>
<tr>
<td>ISS (&gt;42)*</td>
<td>0.001</td>
<td>2.70</td>
<td>1.48–4.95</td>
</tr>
<tr>
<td>12-h base deficit (≥8 vs. &lt;8 meq/L)</td>
<td>0.109</td>
<td>1.55</td>
<td>0.91–2.65</td>
</tr>
<tr>
<td>ED GCS (≥8 vs. &gt;8)</td>
<td>0.185</td>
<td>1.99</td>
<td>0.72–5.58</td>
</tr>
<tr>
<td>24-h maximum insulin (U/h)</td>
<td>0.923</td>
<td>0.99</td>
<td>0.94–1.06</td>
</tr>
<tr>
<td>Liver disease/cirrhosis (Y/N)</td>
<td>&lt;0.001</td>
<td>3.28</td>
<td>1.72–6.25</td>
</tr>
<tr>
<td>24-h vasopressor requirement (Y/N)</td>
<td>&lt;0.001</td>
<td>3.69</td>
<td>2.48–5.48</td>
</tr>
<tr>
<td>Exploratory laparotomy (Y/N)</td>
<td>0.481</td>
<td>0.895</td>
<td>0.57–1.29</td>
</tr>
<tr>
<td><strong>MOF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early hyperglycemia (Y/N)</td>
<td>0.034</td>
<td>1.29</td>
<td>1.02–1.62</td>
</tr>
<tr>
<td>Gender (F vs. M)</td>
<td></td>
<td></td>
<td>0.45–0.76</td>
</tr>
<tr>
<td>12-h blood Tx requirement (≥6 vs. &lt;6 U)</td>
<td>&lt;0.001</td>
<td>2.07</td>
<td>1.63–2.62</td>
</tr>
<tr>
<td>ISS (25–41)*</td>
<td>0.006</td>
<td>1.52</td>
<td>1.12–2.04</td>
</tr>
<tr>
<td>ISS (&gt;42)*</td>
<td>0.003</td>
<td>1.70</td>
<td>1.20–2.39</td>
</tr>
<tr>
<td>12-h base deficit (≥8 vs. &lt;8 meq/L)</td>
<td>0.258</td>
<td>1.17</td>
<td>0.89–1.53</td>
</tr>
<tr>
<td>ED GCS (≥8 vs. &gt;8)</td>
<td>0.199</td>
<td>1.17</td>
<td>0.92–1.50</td>
</tr>
<tr>
<td>24-h maximum insulin (U/h)</td>
<td>0.050</td>
<td>1.04</td>
<td>1.00–1.09</td>
</tr>
<tr>
<td><strong>NI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early hyperglycemia (Y/N)</td>
<td>0.470</td>
<td>1.08</td>
<td>0.87–1.34</td>
</tr>
<tr>
<td>ISS (25–41)*</td>
<td>&lt;0.001</td>
<td>1.61</td>
<td>1.24–2.10</td>
</tr>
<tr>
<td>ISS (&gt;42)*</td>
<td>0.002</td>
<td>1.64</td>
<td>1.20–2.25</td>
</tr>
<tr>
<td>12-h base deficit (≥8 vs. &lt;8 meq/L)</td>
<td>0.140</td>
<td>1.19</td>
<td>0.94–1.51</td>
</tr>
<tr>
<td>ED GCS (≥8 vs. &gt;8)</td>
<td>0.020</td>
<td>1.30</td>
<td>1.04–1.34</td>
</tr>
</tbody>
</table>


ISS, Injury Severity Score; ED, emergency department; GCS, Glasgow Coma Scale score; Tx, transfusion.

### REFERENCES

Early Hyperglycemia and Multiple Organ Failure


**DISCUSSION**

**Dr. Jeffrey Guy** (Nashville, Tennessee): Stress-induced hyperglycemia has been described in the literature for approximately 150 years. Hyperglycemia can be attributed to the production of endogenous catecholamines, proinflammatory cytokines, and nervous system signals on metabolic pathways. These pathways are activated and regulated secondary to the stress of injury. An injured patient may experience hyperglycemia shortly after injury and prior to being initiated to an insulin regimen upon admission to the intensive care unit.

Dr. Sperry and colleagues sought to determine if early hyperglycemia was a marker of poor outcome in critically injured patients. In the present series, the authors demonstrated that early hyperglycemia, as defined by a maximal blood sugar in the first 24 hours of greater than 200 milligrams per deciliter, was associated with a higher mortality and rate of MOF.

The initial trials performed by van den Berghe demonstrated that intensive glucose control had the greatest impact on in-hospital mortality by reducing death caused by multiple organ dysfunction with a septic focus. However, in this series, patients who experienced an increased blood glucose within 24 hours of admission and were subsequently placed on an intensive and identical insulin protocol did not have an increased rate of nosocomial infections.

Few clinicians would disagree that the presence of hyperglycemia in a critically ill or injured patient results in a worse outcome. Gone are the days of ignoring hyperglycemia and attributing the elevated blood glucose to an adaptive stress response. I have several questions for the authors.

Number one, as you have outlined in your article, in previous investigations on the effect of hyperglycemia, sepsis has been an essential contributing factor for the development of multiple organ dysfunction and death. The current investigation demonstrates that hyperglycemia resulted in an elevated mortality, but not an increased rate of nosocomial infections or infectious complications. How do you explain this?

Number two, in the early phases of critical illness, hepatic gluconeogenesis is increased secondary to increased plasma concentrations of hormones such as glucagon, cortisol, and growth hormone. Increased plasma concentrations of catecholamines, such as epinephrine and norepinephrine, promote hepatic gluconeogenesis and subsequently increase blood glucose levels. Furthermore, sympathomimetics also increase insulin resistance within the peripheral tissues.

Regarding sympathomimetic vasopressors in the first 24 hours, 32.8% of those in the early hyperglycemic group were administered vasopressors, compared with only 14% in the non-early hyperglycemia. What is the role of exogenous catecholamines and hyperglycemia and the contributor of vasopressor administration to hyperglycemia, as well as mortality rate in this series?

The third question is in regard to the fact that in the early hyperglycemia group, 53% of the patients required laparotomy and 18% required some form of thoracotomy. Of those without early hyperglycemia, only 4% required laparotomy and 8% required thoracotomy. What percentage of those surgeries occurred upon admission or in the first 24 hours of admission to the trauma center? Is a glucose regimen instituted in the operating room by anesthesia?
The early hyperglycemia group received twice as much blood transfused in the first 12 hours. Please explain the contribution of transfusion to the development of early hyperglycemia, as well as the increased morbidity and mortality in trauma patients.

You tested if early hyperglycemia was an independent risk factor for MOF; NI, and mortality after “adjusting for important confounders”. What were those confounders? Specifically, were the need for surgery, vasopressor use, and transfusion considered? Should the variables also be considered as potential risk factors for subsequent mortality and death in trauma patients?

The authors are to be congratulated on contributing to a growing body of literature on the adverse effects of hyperglycemia in the critically ill and injured. A clear consensus guideline is lacking in the published literature on how to achieve and maintain euglycemia. A lack of consensus guidelines contributes to clinical failure in preventing hyperglycemia.

Dr. Jason Sperry (Dallas, Texas): In regard to sepsis in our injured cohort, the main question is what came first, infection and then organ failure or organ failure and then subsequent infection. At least in this severely injured trauma cohort, MOF occurred early, within the first 2 to 4 days in most cases, well prior to the majority of the infectious outcomes. This was why we used Cox proportional hazard regression and Kaplan–Meier analysis and incorporated time of event into the analysis to pan out those differences and adjust for early mortality so as not to obscure our outcomes of interest.

The second question regarding the acute phase response following injury, we agree with you on this and realized that early hyperglycemia after injury is associated with endogenous production of growth hormone, endogenous steroids, and endogenous catecholamines and importantly we realized early vasopressors may be an important confounder to adjust for. Almost 20% to 30% of our patients required vasopressors within the first 24 hrs after injury. We did control for that in all of our multivariate analyses. We realize that could have been a very important potential confounder.

You bring up the differences in operative interventions, which was also very interesting to us, and it almost strengthens our argument that these early hyperglycemic patients have a higher mortality rate, but those that ultimately survive, and we attempted to adjust for that using our statistical methods, should have more interventions, and they have greater resuscitation requirements and higher blood transfusion requirements, which are all associated with worse outcomes and nosocomial infections in prior literature.

These patients, at least by our statistical methods, don’t have a higher rate of NI and we’re attributing that to strict glycemic control. This article does not prove that it’s strict glycemic control. Again, as discussed in the article and in my presentation, there are other SOPs. One in particular is to restrict a transfusion trigger that may be responsible for an overall reduction in infection risk.

There’s also ventilator-associated management guidelines, but that’s why we looked at different infection subtypes. UTI, catheter-related bloodstream infection, and pneumonia, to make sure that this was an overall reduction in infection risk.

If we were to attribute these findings or differences compared with prior literature, it has to be something that is globally reducing infection risk. It’s probably the strict glycemic control protocol regimen.

I agree with your comment on the differences in blood transfusions. Early hyperglycemic patients are more severely injured and have greater resuscitation requirements and that includes crystalloid, blood, and a higher incidence of early vasopressor requirement, and they’re more severely injured.

These two groups are very different. Early hyperglycemic patients are under extreme physiologic insult by our data. They’ve been more severely injured and they’re a totally different cohort of patients. Interestingly though, there doesn’t seem to be a higher rate of NI when you try to control for differences in mortality and important confounders.

Your last question was pertinent to our selection of covariates in our multivariate models. We used a 5% change in estimates approach. Our most important covariate that we were looking at was early hyperglycemia in our models.

Based on a 5% change in estimates approach, we selected those that had an effect or that were important in changing the odds ratio for early hyperglycemia and so we selected the important confounders for the association between early hyperglycemia and the outcome of interest. Those included different comorbidities and they were different for each outcome of interest. Our covariates changed depending on the covariate, the outcome of interest that we were looking at the time.

We included vasopressor use, operative intervention, whether it was abdominal or thoracic, and insulin requirements. This was independent of the dose of insulin that they received, the maximum dose of insulin per hour that they received in the first 24 hours.

One data point that I did not have access to and that was not recorded was the time to operative intervention, but primarily, these patients are a significantly severely injured cohort with a mean overall Injury Severity Score of 32, which is higher than typical studies published. The large majority was operated on within the first 24 hours, but I don’t have data to back that up, actually.
Intensivist Bedside Ultrasound (INBU) for Volume Assessment in the Intensive Care Unit: A Pilot Study

Brendan G. Carr, MD, MA, Anthony J. Dean, MD, Worth W. Everett, MD, Bon S. Ku, MD, Dustin G. Mark, MD, Olugbenga Okusanya, BA, Annamarie D. Horan, PhD, and Vicente H. Gracias, MD

**Background:** Estimation of volume status in the high-acuity surgical population can be challenging. The use of intensivist bedside ultrasound (INBU) to rapidly assess volume status in the surgical intensive care unit (SICU) was hypothesized to be feasible and as accurate as invasive measures.

**Methods:** Clinician sonographers (CSs) were trained to perform basic cardiac ultrasound and sonographic assessment of the inferior vena cava (IVC). A convenience sample of general surgery and trauma patients was enrolled in the SICU. The CS interpreted IVC and cardiac parameters and then categorized the subject as hypovolemic or not hypovolemic. Intensivists caring for the patients were blinded to the INBU findings and made a real-time expert clinical judgment (ECJ) of the patient’s volume status (hypovolemic vs. not hypovolemic) using all available traditional data.

**Results:** A total of nine CSs performed 70 studies; three of the CSs performed the majority of the studies (86%). Adequate ultrasound (US) views for cardiac and IVC assessment were obtained in 96% and 89% of studies, respectively. The ECJ was considered to be the standard to which comparisons were made. The concordance rate between ECJ and central venous pressure was 62%. ECJ concordance with sonographic measures were similar (cardiac US = 75%, IVC US = 67%, and IVC collapse index = 65%). All pairwise comparisons against the ECJ/CVP agreement were not significantly different.

**Conclusions:** INBU is feasible in the SICU and is equivalent to central venous pressure in assessing volume status. Noninvasive methods to assess volume status may decrease the need for invasive procedures.

**Key Words:** Ultrasound, ICU, Intensivist, Hypovolemia, Volume.


Estimation of volume status and cardiac function in the high-acuity surgical population can be challenging. Overestimation of fluid requirements can lead to a variety of complications including pulmonary edema, abdominal hypertension, and compartment syndromes. Conversely, underestimation of volume status can lead to persistent hypovolemia with resultant hypoperfusion or unrecognized shock and subsequent end-organ failure. Methods currently used to determine volume status include central venous pressure (CVP) monitors, pulmonary artery catheters, esophageal doppler, transesophageal echocardiography, and transthoracic echocardiography. Historically, invasive monitoring devices have been considered to be the standard for assessing volume status, but there is no consensus on their indications or accuracy. In addition, invasive methods have potential morbidities associated with their use. The potential for noninvasive methods to estimate volume status and cardiac function is highly appealing.

The use of ultrasound (US) by clinician sonographers (CSs) has been well documented for various purposes only after brief, focused training periods. The feasibility and utility of cardiac US by CS to determine ejection fraction has been demonstrated.

Sonographic measurement of inferior vena cava diameter (IVCD) has primarily been used to estimate volume status in patients undergoing hemodialysis and others. Categorical IVCD measures have suggested a range of diameters for the identification of abnormally low or high CVP, with low CVP increasingly likely as IVCD gets smaller than 1 cm, and abnormally high CVP increasingly likely as IVCD increases above 2 cm. IVCD variation may be complicated by positive-pressure ventilation, and no consensus exists regarding absolute measurements defining hypovolemia.

Another parameter that has been assessed as a measure of intravascular volume status is inferior vena cava (IVC) collapse index (IVC-CI). Under normal conditions in healthy subjects, the IVC displays respiratory variation in diameter, with larger diameter in expiration, and smaller diameter during inspiration. There is no consensus on an exact IVC-CI cutoff for hyper- or hypovolemia.
Volume estimation using a combination of cardiac US and IVC measurement has been described in the pediatric population. To our knowledge, there has been no investigation into the feasibility or accuracy of combined IVC and cardiac US for volume assessment performed by CS in critically ill surgical patients. We performed a pilot study in which we hypothesized that intensivist bedside ultrasound (INBU) would be feasible and as accurate as invasive measurements in the determination of intravascular volume status in surgical intensive care unit (SICU) patients.

PATIENTS AND METHODS

This was a prospective cross-sectional study of a convenience sample of SICU patients performed at an urban 695-bed tertiary care Level I trauma center. The SICU is a 56-bed unit with an average admission Acute Physiology and Chronic Health Evaluation (APACHE) III of 51. It is staffed at all times by a board-certified intensivist. The University of Pennsylvania Institutional Review Board approved this study with a waiver of informed consent and Health Insurance Portability and Accountability Act waiver as authorized by Title 45 Code of Federal Regulations Part 46.116 (d) and Part 164.512 (i), respectively.

CSs were surgical critical care faculty, surgical critical care fellows, emergency medicine faculty, and emergency medicine fellows and residents. All CSs attended a 3-hour didactic and practical training session developed by the emergency medicine ultrasound fellowship director (A.J.D.). After training, CSs were required to perform a minimum of 25 supervised USs before study data collection. Examinations were conducted with a C15 4 MHz to 2 MHz tightly curved array transducer on a portable US unit (Sonosite Titan, Sono, Inc., Bothwell, WA). CSs were not privy to the details of the patient’s clinical course, laboratory values, or other diagnostic information.

Data were recorded using a standardized data collection form from January 1, 2006, to May 24, 2006. Data included patient demographics, US measurements, CS qualitative assessments, and CVP. Concurrent with INBU, intensivists caring for each patient made a real-time expert clinical judgment (ECJ) of the patient’s volume status (hypovolemic [Hypo] vs. not hypovolemic [NHypo]) using all available data, including the patient’s history, current examination, and invasive monitoring data. Intensivists were blinded to the US findings until after they had recorded their impression of volume status.

IVC US

The sonographic evaluation of the IVC involved examination at a level approximately 2 cm below the junction of the hepatic veins, as described in previous studies of this topic. In the transverse and longitudinal orientation, M-mode images were obtained, and maximal and minimal measurements made. While these measurements often correlated with expiration and inspiration respectively, no attempt was made to correlate these with the respiratory cycle, since in intubated patients this relationship may be reversed.

Sonographic views of the IVC were obtained using the liver as a sonographic window via either the epigastrium or the right intercostal spaces. Choice of either (or both) of these was based on available sites for probe placement (limited by patient habitus, dressings, or wounds) and CS preference. As previously noted, measurements of maximal and minimal diameter were made without regard to the respiratory cycle. The IVC-CI was calculated according to the standard formula IVC-CI = \[ \frac{\text{IVC}_{\text{max}} - \text{IVC}_{\text{min}}}{\text{IVC}_{\text{max}}} \] where IVC-CI is the maximum IVC and IVC-CI is the minimum IVC. At the completion of the examination, CSs recorded their impression of intravascular volume status based on the IVC-CI as well as qualitative considerations such as overall IVCD, the appearance of a “slit like” IVC, or a ratio between anteroposterior and lateral IVCDs of less than one-third. On the basis of qualitative and quantitative information from their IVC assessment, the CS recorded an impression of intravascular volume status as Hypo or NHypo.

Cardiac US

The cardiac US evaluation involved examining the heart in as many of five standard views as were available (limited by habitus, dressings, or wounds). The five views sought were parasternal long axis, parasternal short axis, subxiphoid four chamber, subxiphoid short axis, and apical four chamber. On the basis of the cardiac examination, CSs estimated intravascular volume status. Patients were considered to be Hypo if either hyperdynamic cardiac function or end-systolic left ventricular collapse were present. The patient was deemed to be NHypo if these findings were not present on the cardiac examination.

Data Analysis

Data were analyzed using Stata (version 9.0 SE, College Station, TX). ECJ was used as a surrogate standard for volume status. CVP was established a priori as a comparison standard against which other measures of volume status would be compared. Concordance rates with 95% confidence intervals were assessed comparing ECJ with CVP (Hypo: CVP ≤8 cm H2O; NHypo: CVP >8), cardiac US, IVC visual estimation, and IVC-CI (cutoff between Hypo and NHypo was set at IVC-CI = 50%). Comparisons of concordance rates were performed using two-sample tests of proportions. A p value of <0.05 represents a statistically significant finding. All subgroup analysis is exploratory given the pilot nature of the study.

RESULTS

A total of 70 studies were performed by nine different investigators. Three of the CSs performed 86% of the US studies. ECJ was rendered regarding volume status by 15 different intensivists. The ECJ data were missing for 1/70
INBU for Volume Assessment in the ICU

Table 1 Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>52.3 ± 18.2</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>37 (53)</td>
</tr>
<tr>
<td>CVP, n (%)</td>
<td>62 (89)</td>
</tr>
<tr>
<td>PA catheter, n (%)</td>
<td>16 (23)</td>
</tr>
<tr>
<td>Intubated, n (%)</td>
<td>41 (59)</td>
</tr>
</tbody>
</table>

(1.4%) of the studies. One of the intensivists contributed 21% of the ECJ data. Patient demographics are shown in Table 1.

A cardiac window adequate for making a volume assessment could be obtained in 96% of the studies. The parasternal long-axis view was the most preferred view and was obtained in 98% of the studies. The parasternal short-axis view was the second most used view (96%), followed by the apical four chamber (74%), the subxiphoid four chamber (35%), and the subxiphoid short-axis (18%). The IVC could be visualized and measured in 89% of cases.

The agreement rate between ECJ and CVP was 62%. Agreement rate between ECJ and cardiac US was 75%. Agreement rate between ECJ and IVCD was 67%. Agreement rate between ECJ and IVC-CI was 65% (Table 2). All pairwise comparisons against the ECJ/CVP agreement were not significantly different (ECJ/CVP vs. ECJ/IVCD p = 0.56, ECJ/CVP vs. ECJ/IVCD-CI p = 0.72). There was a nonsignificant trend toward increased reliability of cardiac US compared with CVP (ECJ/CVP vs. ECJ/cardiac US p = 0.11). Concordance rates were not significantly different when intubated and nonintubated patients were analyzed separately.

In intubated patients, the trend toward significance for the concordance between ECJ/CVP and cardiac US was even stronger (p = 0.08) (Table 3).

DISCUSSION

Our pilot study suggests that INBU in the SICU is feasible and potentially useful. We used intensivist ECJ of volume status as a gold standard, and, for reference, we determined the concordance between manometric CVP measurement and ECJ. We then compared INBU concordance rates with this reference standard. We demonstrated that, after a brief training program, CS estimates of intravascular volume are as predictive of ECJ as static CVP.

ECJ of volume status draws on many clinical parameters. This is reflected by the fact that ECJ was not concordant with CVP in more than one-third of cases. Global impressions of the patient’s clinical condition and trends in invasive monitoring information are important factors. We think that INBU will add to the armamentarium of the clinician, offering a valuable additional data point to clinician judgment. INBU is noninvasive, rapid, repeatable, and is performed at the bedside. Results are available in real time, thus avoiding the delays associated with radiology or cardiology performed US.

One of the primary aims of this analysis was to demonstrate the feasibility of this technique. The CSs enrolling patients in this study were from various medical specialties and were largely inexperienced in obtaining ultrasonographic windows in the ICU. Patients in the SICU have various wounds and dressings, which may obscure US views. In addition, these patients are often difficult to position adequately because of the constraints of indwelling devices including endotracheal tubes, chest tubes, and abdominal drains. Despite this, we were able to obtain adequate cardiac and IVC measurements in almost all subjects.

A second aim of the study was to compare volume assessment by INBU with that obtained by established measures. CVP is one such measure and served as a reference for comparison. We demonstrate comparable agreement between four assessments of volume status and ECJ (CVP, cardiac US, IVCD, and IVC-CI). The ability to assess volume status by evaluating cardiac filling and function is not surprising given previous data. Although measuring IVCD has not been widely used in the ICU population, many cardiologists report IVC plethora or collapse when performing formal echocardiography. INBU is promising as a means by which to reinforce clinical judgment without performing invasive procedures. The IVC-CI is rooted in IVC physiology. During the normal respiratory cycle, negative intrathoracic pressure on inspiration results in collapse of the intra-abdominal portions of the IVC, whereas the reverse occurs in expiration.

Table 2 Concordance Rates and 95% Confidence Intervals Between ECJ and Markers of Hypovolemia

<table>
<thead>
<tr>
<th></th>
<th>CVP (n = 62)*</th>
<th>Cardiac US (n = 67)*</th>
<th>IVUS (n = 61)*</th>
<th>IVC-CI (n = 62)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECJ Pairwise comparisons vs. ECJ/CVP</td>
<td>62% (48–73)</td>
<td>75% (63–84)</td>
<td>67% (53–79)</td>
<td>65% (51–76)</td>
</tr>
<tr>
<td></td>
<td>p = 0.11</td>
<td>p = 0.56</td>
<td>p = 0.72</td>
<td></td>
</tr>
</tbody>
</table>

* n varies because of missing data.

Table 3 Concordance Rates and 95% Confidence Intervals Between ECJ and Markers of Hypovolemia in Intubated Patients

<table>
<thead>
<tr>
<th></th>
<th>CVP (n = 39)*</th>
<th>Cardiac US (n = 40)*</th>
<th>IVUS (n = 34)*</th>
<th>IVC-CI (n = 35)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECJ Pairwise comparisons vs. ECJ/CVP</td>
<td>56% (40–72)</td>
<td>75% (58–87)</td>
<td>65% (46–80)</td>
<td>63% (45–79)</td>
</tr>
<tr>
<td></td>
<td>p = 0.08</td>
<td>p = 0.43</td>
<td>p = 0.54</td>
<td></td>
</tr>
</tbody>
</table>

* n varies because of missing data.
Abnormally low CVP is increasingly likely as IVC-CI approaches 100%, and abnormally high CVP is increasingly likely as IVC-CI approaches 0% (Figs. 1 and 2). During positive-pressure ventilation, intrathoracic pressures may impact IVC variation. This is a pilot study and has limitations. Although we performed 70 studies, the majority were enrolled by three of the nine investigators. These investigators have more (non-ICU) experience and expertise with US than most intensivists. It is possible that similar results would not be obtained if a more diverse group of CS-enrolled patients. Our choices of reference and comparison standards may also be problematic.

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We allowed intensivists to identify volume status using all available clinical parameters. We used a dichotomized measure of ECJ (Hypo vs. NHypo) as our reference standard. Although this allowed us to make comparisons, hypovolemia exists on a continuum and this information was lost. Further, ECJ is not a validated and repeatable standard and as such introduces substantial error into the model. Finally, we did not attempt to validate our sonographic determination by following the patient’s course or measuring biochemical or clinical parameters. For our comparison standard, we calculated agreement between CVP and ECJ. Despite many shortcomings, CVP is widely used, readily understood, and was available in the majority of our study group. In addition, we compared static sonographic volume estimates to a static invasive measure (CVP). In clinical practice, volume assessment by invasive means is dependent on recognition of trends. Similarly, we anticipate that INBU will be most useful in monitoring trends in patient condition and responses to therapeutic interventions.

Other limitations of this study arise from the dynamic nature of real-time bedside US. No attempt was made to control for CS preferences regarding US windows. Any one or more of five possible cardiac views were obtained, and IVC views were obtained through both intercostal and epigastric windows. Although this may be a limitation of study design, it reflects the flexibility afforded a treating physician performing US at the bedside.

It was anticipated that an important consideration in determining volume status using INBU would be the patient’s intubation status. Our pilot data suggest that IVC-CI and IVCD may not be significantly influenced by this variable. In view of conflicting previous reports on this topic, a larger study is needed to confirm the findings in this pilot investigation. A trend toward significance was noted for the cardiac US. This could be because positive pressure decreased the strength of the relationship between the CVP and the ECJ or because cardiac US is particularly helpful for patients on positive-pressure ventilation. Further research investigating the relationship between cardiac US and positive-pressure ventilation is warranted. Finally, for the purpose of this study, volume status was collapsed into dichotomous categorical variables (Hypo or NHypo). Although this is clinically important information, volume status exists on a continuum and a larger study may reveal that hypervolemic states are also identifiable using this technique.

The use of US by noncardiologist, nonradiologist clinicians is not novel, and there has been increasing interest in the critical care community. INBU provides a noninvasive and rapid means of acquiring clinical information. Serial examinations can be performed to measure clinical trends and guide ICU interventions. We describe two techniques that were used to estimate volume status, but applications for INBU in critically ill patients extend beyond those reported here. Bedside sonographers can use US to detect pleural and pericardial effusions, cardiac tamponade, pneumothorax, pulmonary consolidation, fluid collections, and ejection fraction. This pilot study suggests that using US to estimate volume status is feasible. In addition, CSs who were blinded to details about the patient were still able to use...
INBU to detect hypovolemia as accurately as the common invasive criterion of CVP. We would expect that in the hands of intensivists knowledgeable about their patients, INBU would be even more effective. Larger prospective trials investigating the use of clinician-performed US in the assessment of hemodynamic status of critically ill patients should be explored.

REFERENCES

10. NHLBI ARDS Clinical Trials Network. Pulmonary-artery verses invasive criterion of CVP. We would expect that in the hands of clinician-performed US in the assessment of hemodynamic status of critically ill patients should be explored.
11. NHLBI ARDS Clinical Trials Network. Pulmonary-artery verses invasive criterion of CVP. We would expect that in the hands of clinician-performed US in the assessment of hemodynamic status of critically ill patients should be explored.
DISCUSSION

Dr. Mark Mckenney (Miami, Florida): The group at the University of Pennsylvania is the first to evaluate intensivist-performed ultrasound in the surgical intensive care unit for adequacy of resuscitation. Their hypothesis is an intensivist bedside ultrasound could be used to rapidly and accurately assess volume status.

Nine clinicians performed 70 studies during a period of 5 months in their large surgical intensive care unit. They had Institutional Review Board approval and they had waiver of consent and waiver of Health Insurance Portability and Accountability Act (HIPAA) form. These seem reasonable.

They compared ultrasound to clinical judgment as the gold standard and used central venous pressure (CVP) as a surrogate marker in an accepted test to determine volume status. The advantages of a noninvasive method to monitor what an invasive method can do are self-evident, but the noninvasive method must be accurate, available, repeatable, and easy to perform.

Easy performance is actually extremely critical. Although central venous catheters are placed by intensivists, the follow-up parameters are recorded by the bedside intensive care unit nurse and require limited physician input.

The authors compare clinical judgment to four parameters: (1) CVP; (2) inferior vena cava diameter; (3) inferior vena cava (IVC) collapse index; and (4) cardiac ultrasound. The authors found that intensivist bedside ultrasound was not statistically different than CVP compared with the gold standard of clinician judgment.

I have five questions. Question one, in your conclusion, you state intensivist bedside ultrasound is rapid, but there are no times given to support this statement. Could you please give us the time frames in which this was accomplished? Question two, patients were classified as hypovolemic and not hypovolemic. Why weren’t there more classifications on this? Patients can also be fluid overloaded or hypervolemic. Question three, there were 70 studies, but how many patients did this involve? Question four, IVC diameter was measured at maximum inspiration. Was this true for both intubated and extubated patients? Question five—and probably the most important—are you using this clinically now?

In conclusion, the authors took a novel and timely concept and have expanded it into the surgical intensive care unit. This shows great promise and they are to be congratulated for putting this test into practice. More work is needed still though.

Dr. Brendan Carr (Philadelphia, Pennsylvania): In regard to the first question about the duration of time to acquire adequate images and to make an assessment using ultrasound, the answer is we did not ask our sonographers to record the time and we did not ask our research staff to mark them as they went into the room. On the next rendition, we have asked for that to happen, but I don’t have an answer for you yet. I can tell you anecdotally that there is a learning curve and it started probably around 10 minutes and has whittled itself down to 5 or so.

The second question, why did we call the patients hypovolemic or not hypovolemic? In fact, we had the sonographers and the intensivists respond on a Likert scale for us, which we then had to dichotomize, primarily because of numbers and, in addition, because of interpretability.

We agree that measuring volume status as a static measure and calling people hypovolemic and not hypovolemic is oversimplifying a very complex issue.

There were 70 studies performed and your question was how many patients it involved. The reason that studies and patients aren’t the same is because someone could come in the morning—it’s a convenience sample—so one of the clinician sonographers could come in the morning and ask the intensivists taking care of the patient their opinion, and do their ultrasound, and then another sonographer could come later that afternoon.

The answer is 54 or so, 54–56. There were not that many repeats and they clearly had a separate intensivist judgment made at the time that the repeat ultrasound was performed.
You asked about IVC diameter and when we measured it. In nonintubated patients, the data is pretty straightforward that in inspiration you measure a minimum diameter and in expiration a maximum diameter. There is some suggestion in intubated patients that this changes, that it might be reversed.

We didn’t see that it was reversed. We measured in intubated patients without regard to the respiratory cycle. We measured maximum and minimum, primarily because it simplifies the technique and we thought the simpler the better, if it works and we can use it. A complex technique is not what any of us are looking for.

Then the last question is, are we using it clinically? The answer is not really, and in large part, that’s because of who was trained. There were very few folks trained in the technique and many of them have moved on in one capacity or another.

We trained fellows and a new faculty member. We, number one, have not had the opportunity to publish our work or to present our work in a forum to get feedback or to present our work in a forum to get feedback and whether we should be starting to consider this information available?

Dr. Lawrence Lottenberg (Gainesville, Florida): I have a couple of comments. The photos you showed were from a very nice Siemens’ ultrasound machine. You commented that you used the SonoSite TITAN to do your studies. I was wondering why you didn’t show any SonoSite pictures as far as your reconstructions.

The second comment, there are several other “noninvasive” pieces of machinery available, which tend to give us more of a global picture of what’s happening.

One thing that I was a little concerned about is it looked like you were just taking a snapshot in time and not going back and seeing if there was a change in your numbers as you changed your resuscitation. For instance, the esophageal Doppler, which measures flow corrected time across the aortic route, allows you to have a continuous picture of changing over time as your resuscitative strategies are changing.

How do you propose to use this methodology to do the same?

Dr. Brendan Carr: With respect to the photos, I apologize. I have a large databank of ultrasound images and I took from them examples that I thought would be instructive.

Then with respect to the first question, I think this is the greatest strength of ultrasound, the piece that you’re bringing up here, is that it’s easy. It is located in the intensive care unit and I can pick it up whenever I want and put it on the heart and measure what happens in real time as I resuscitate the patient.

In my mind, this is everything that the esophageal Doppler is and potentially more. As I resuscitate the patient and watch them evolve, I think that this becomes a very, very important piece of technology for me to have available.

We didn’t do it in the study and in fact, we recognize that measuring a static CVP measure is very limited. Most of us think about the trend as being something that we rely on pretty heavily for volume status assessment. Again, some of this is methodological. We wanted to simply ask can we do this and what’s the simplest way we can measure that, and clearly we will proceed from here.

Dr. Michael A. West (Chicago, Illinois): The one question that I wanted to ask is in regard to your use of the intensivist opinion, as the gold standard, of what the volume status was and as a senior attending intensivist, I certainly appreciate the adoration that goes with that, that we have the answer.

I wonder if you did any examination of what the inter-intensivist variability might be in that assessment, given that you’ve got a 65% correlation with the expert and your CVP or your bedside ultrasound examination and you’re just taking the intensivist opinion as the gold standard and was there in fact any variability, in that there was an approximately 80% correlation between the different intensivists, given the information available?
Then, as a kind of a follow-up on that, given that expert opinion or the assessment made at that time, was it in fact correct or not correct, based on the subsequent course during the next several hours, as to whether that was the right judgment or not, that they needed fluid or they needed diuresis or whatever?

Dr. Brendan Carr: Those are great additions to the methodology that I wish I had incorporated. We relied on the intensivist caring for the patient, because we thought they had the best sense of the patient’s course, the patient’s care that had been provided, the direction the patient was going, and the patient’s volume status. No, we didn’t ask a separate intensivist, but it would not be difficult to do, given the size of the group, and I think that you’re right. We should do it.

Whether we followed the patients to term and whether the intensivist’s judgment was correct, again the answer is no, but, again, the answer should be, I think, and can be in the future, yes. I think those are wonderful additions to our methodology that we’ll incorporate.
β-Blocker Exposure in Patients With Severe Traumatic Brain Injury (TBI) and Cardiac Uncoupling

William P. Riordan Jr, MD, Bryan A. Cotton, MD, Patrick R. Norris, PhD, Lemuel R. Waitman, PhD, Judith M. Jenkins, MSN, and John A. Morris, Jr, MD

Background: Cardiac uncoupling and reduced heart rate (HR) variability are associated with increased mortality after severe traumatic brain injury (TBI). Recent data has shown β-blocker (BB) exposure is associated with improved survival in this patient population. The purpose of the present study was to evaluate the effect of BB exposure on the mortality risk of patients with severe TBI and early cardiac uncoupling.

Methods: From December 2000 to October 2005, 4,116 patients were admitted to the trauma intensive care unit. Four hundred forty-six patients (12%) had head Abbreviated Injury Scale score ≥5 without neck injury and had continuous HR data for the first 24 hours. One hundred forty-one patients (29%) received BB. Cardiac uncoupling was calculated as the percent of time that 5-minute HR standard deviation was between 0.3 bpm and 0.6 bpm on postinjury day 1.

Results: A relationship between BB and survival was observed when the population was considered irrespective of length of stay or BB start time (p < 0.001). Cardiac uncoupling appears to stratify patients into groups who might receive additional benefit from BB, and identifies patients with increasing mortality. However, the association of BB with survival was attenuated when analyses accounted for selection bias in BB administration.

Conclusions: BB exposure was associated with reduced mortality among patients with severe TBI. Though loss of HR variability has previously been associated with an increase in mortality, BB exposure appears to be associated with increased survival across all stratifications of cardiac uncoupling.

Key Words: Heart rate variability, Cardiac uncoupling, β-Blocker, Trauma, Brain injury.

Selection of Participants

As shown in Figure 1, the study population consists of all trauma admissions to VUMC who (1) were admitted to the trauma intensive care unit (ICU) from December 2000 through November 2005 within 24 hours after emergency department arrival, (2) had severe head injury (AIS score \( \geq 5 \)), (3) did not have a significant neck injury (International Classification of Diseases, [ICD]9 codes 806.00–806.19), and (4) had sufficient HR data (\( \geq 12 \) hours) in the first 24 hours of ICU stay (N = 446).

There are several reasons why 100% data capture was not achieved for all ICU admissions. First, Signal Interpretation and Monitoring (SIMON) was not operational on all trauma ICU beds during the entire study period (4 of 14 beds through June 2001, 10 of 14 beds through July 2003). In addition, ICU admission counts are derived from Trauma Registry of the American College of Surgeons (TRACS), which may include trauma admissions to other ICUs under overflow situations. Finally, we required at least 12 hours of data within the first 24 hours for reliable computation of integer HRV, thus excluding patients who die soon after arrival, are discharged from the ICU, or who spend extended time out of the ICU for operative procedures or radiologic studies.

Data Sources

Data were extracted and linked from the following three systems, then deidentified:

**SIMON**

The SIMON system continuously records all physiologic data from bedside monitors in the VUMC trauma ICU. Parameters are sampled once every 1 to 4 seconds, and include HR, blood pressure, intracranial and cerebral perfusion pressures, arterial and mixed venous oxygen saturations, temperature, and pulmonary artery catheter data.

**TRACS**

Parameters captured via participation in the TRACS include demographics, injuries, operative procedures, disposition, complications, and LOS. SIMON and TRACS meet regulatory requirements for data repository status, and are approved by the Vanderbilt University Institutional Review Board. Data requests are processed in accordance with institution and Health Insurance Portability and Accountability Act regulations.

**Care Provider Order Entry (CPOE)**

WizOrder (Vanderbilt University, Nashville, TN) is a custom application used for all inpatient medication, consultation, and transfer orders. Data captured includes medication, dose, route of administration, ordering provider, and order time.

Definitions and Measurements

**Registry Variables**

The TRACS registry was queried for patient age, gender, Injury Severity Score (ISS), arrival time, discharge time, and outcome.

**\( \beta \)B Exposure and Start Time**

\( \beta \)B exposure was determined by referencing the American Hospital Formulary Society classification. Medication orders in the CPOE system were matched to the corresponding dispensed product from the medical center pharmacy system. All drugs with the American Hospital Formulary Society classification 24:24 (\( \beta \)-adrenergic blocking agents) were included as \( \beta \)Bs. The following medication orders were included in the study: esmolol, propranolol, labetalol, metoprolol, atenolol, and carvedilol. Exposure to \( \beta \)B was defined as orders for propranolol (injection or oral), metoprolol (injection or oral), or labetalol or esmolol infusion. \( \beta \)B administration used primarily in conjunction with operative procedures, defined by both drug and route, was excluded. Time of initial \( \beta \)B exposure was defined as the earliest medication start time as recorded in the hospital CPOE system. Indications for \( \beta \)B administration are not available for analysis as no protocol is currently in place; however, patients who exhibit clinical manifestations of sympathetic storm are typically considered for \( \beta \)-blockade.

**HRV**

The SIMON database was queried to extract HR data for all patients during the first 24 hours of ICU stay. Daily HR data for each patient is divided into 5-minute intervals. The standard deviation (SD) of integer HR is calculated for each 5-minute interval; this yields a measure of short-term HRV, which reflects duration (5 minutes) and magnitude (SD) of variability. SIMON samples HR data from a standard monitor.
A clear relationship between cardiac uncoupling and mortality, as defined above, and those who did not. Demographic, acuity, and outcome variables were compared between groups using the χ² test (categorical variables) or Wilcoxon’s ranked sum test (continuous variables). A significance level of p < 0.05 was used throughout. To determine whether cardiac uncoupling identified patients who might benefit from βB, patients were stratified by degree of cardiac uncoupling: <5%, 5% to <10%, 10% to <20%, and >20% uncoupling within the first 24 hours of ICU stay. The relationship between survival and βB exposure was assessed within each of these strata using the χ² test.

To assess the potential influence of survival-time bias on the association between βB exposure and mortality, we examined the survival curves of the population and the exposure to βB over time. We performed additional analyses conditioned on both LOS and time of first βB exposure as follows: for a given cutoff time, only patients with LOS greater than the cutoff were included. This eliminates patients who may not have had the same opportunity to be evaluated for βB administration, because of death or discharge before the cutoff time. Furthermore, all patients exposed to βB after the cutoff time were excluded. This eliminates patients who may have had additional opportunity to be evaluated for β-blockade as a function of increased time in the hospital (which is associated with increased survival). We repeated this procedure for cutoff times of 24, 48, 72, 96, and 120 hours, examining the association between βB exposure and mortality at each cutoff using the χ² test. In addition, we repeated the conditioned analyses on a subgroup of patients with high cardiac uncoupling (≥5%) in the first 24 hours of ICU stay. To further evaluate the potential of selection bias, we constructed a logistic regression model, which included a propensity score reflecting probability of βB exposure as a function of age, ISS, and LOS.

RESULTS

One hundred thirty-eight patients received βB as defined above. Age, ISS, LOS, and mortality differed significantly between patients who received βB and those who did not. Gender, admission trauma score, admission probability of survival, and cardiac uncoupling did not differ significantly between the two groups (Table 1). Exposure to βB was relatively constant within the first 3 years of the study period, but shows an increasing trend in more recent years (Table 2). A clear relationship between βB exposure and survival was observed when the population was considered independent of LOS or βB start time. Cardiac uncoupling appears to stratify patients into groups that might receive additional benefit from

### Table 1 Demographics, Acuity, Cardiac Uncoupling, and Mortality

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>No β-Block</th>
<th>β-Block</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>446</td>
<td>308</td>
<td>138</td>
<td>0.003</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>30.3 (20.9–44.3)</td>
<td>28.7 (20.6–41.0)</td>
<td>35.8 (23.6–49.7)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>345</td>
<td>232</td>
<td>113</td>
<td>0.126</td>
</tr>
<tr>
<td>Female</td>
<td>101</td>
<td>76</td>
<td>25</td>
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</tr>
<tr>
<td>ISS</td>
<td>38 (30–45)</td>
<td>38 (30–45)</td>
<td>43 (33–50)</td>
<td>0.006</td>
</tr>
<tr>
<td>Trauma score</td>
<td>5 (4–8)</td>
<td>5 (4–8)</td>
<td>6 (4–8)</td>
<td>0.316</td>
</tr>
<tr>
<td>Prob. survival (%)</td>
<td>32 (16–69)</td>
<td>33 (16–70)</td>
<td>32 (16–65)</td>
<td>0.652</td>
</tr>
<tr>
<td>LOS (d)</td>
<td>7.9 (3.8–17.6)</td>
<td>5.6 (2.4–13.0)</td>
<td>17.2 (8.5–24.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uncoupling 1st 24 h (%)</td>
<td>1.38 (0–9.79)</td>
<td>1.40 (0–9.87)</td>
<td>1.36 (0–8.6)</td>
<td>0.966</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>164 (37)</td>
<td>135 (44)</td>
<td>29 (21)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Median and intraquartile ranges are reported for continuous variables.

* p values compare β-blocker with no-β-blocker groups, and were computed using Wilcoxon’s ranked sum test (continuous variables) and the χ² test (categorical variables).

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Patients</th>
<th>No. Exposed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001*</td>
<td>81</td>
<td>19 (23)</td>
</tr>
<tr>
<td>2002</td>
<td>79</td>
<td>16 (20)</td>
</tr>
<tr>
<td>2003</td>
<td>88</td>
<td>19 (22)</td>
</tr>
<tr>
<td>2004</td>
<td>116</td>
<td>50 (43)</td>
</tr>
<tr>
<td>2005†</td>
<td>82</td>
<td>34 (41)</td>
</tr>
<tr>
<td>Total</td>
<td>446</td>
<td>138 (31)</td>
</tr>
</tbody>
</table>

* Includes patients from December 2000.
† Includes patients through the end of the study period (November 2005).
B exposure, and identifies patients with increasing mortality (Fig. 2). Relationships were observed between mortality and LOS, and between time of first B exposure and LOS (Figs. 3 and 4). This suggests the possibility of selection bias in B administration. Because each patient has a different probability of receiving a B based on LOS and other factors, the analysis must be adjusted for selection bias. This was accomplished by conditioning analysis on LOS and time of drug administration (Figs. 5 and 6). The association of B exposure with survival is attenuated when analyses are conditioned on LOS and time of first B exposure (Fig. 5).
effect increases for the first two cutoff points (24 and 48 hours) when only patients with early cardiac uncoupling >5% are analyzed, but does not achieve statistical significance (Fig. 6).

The probability of receiving βB as a function of age, ISS, and LOS was modeled, with the predicted probability of receiving βB used as a propensity score. The use of propensity score generates a pseudo-randomized study; patients who are balanced on age, gender, ISS, and LOS have equal chance of receiving βB. The coefficient of βB was negative, suggesting an improved chance of survival; however, this failed to reach statistical significance. βB exposure trended toward improved survival in the propensity-score adjusted model for death (odds ratio 0.83) but this improvement was not statistically significant. Despite this, the trend is consistent throughout our multiple analyses and suggests a beneficial role for β-blockade in patients with TBI. Of the 164 mortalities, more than 93% (153 of 164) could be directly attributed to severe TBI. Sixty-nine of the mortalities were declared brain dead by apnea testing or other means; 84 died after withdrawal of support.

DISCUSSION

We have shown that improved survival is associated with βB exposure; however, the study is insufficiently powered to demonstrate statistical significance. Furthermore, early exposure to βB appears to be more strongly associated with survival. Finally, in this severe TBI population, the association between βB exposure appears more robust in a high-risk subgroup identified by cardiac uncoupling >5%.

Head injury is the leading cause of death among trauma patients who arrive alive to a trauma center, accounting for almost one-third of all trauma mortalities. Of these, almost 75% of patients will die within the first 3 days after injury. Among patients with longer survival time but fatal outcomes, the individuals are usually younger, have isolated TBI, and undergo craniotomy. The underlying causes of death in the majority of these patients are the result of the primary head injury, manifesting through respiratory failure or cardiovascular dysfunction. Other recent literature demonstrates a strong association between neurologic trauma and the development of non-neurologic organ dysfunction, which appears to be a result of sympathetic hyperactivity.

Acute brain injury has been shown to result in autonomic dysfunction, manifested by decreased HRV. In the late 1970s, Lowensohn et al. employed fetal HR monitoring techniques in a neurosurgical ICU to study the influence of acute brain injury on HRV. They observed a reduction of normal cyclic changes in HR in the presence of severe brain damage, and noted a rapid decline in HRV with rising intracranial pressure. They noted that even when intracranial pressure was restored to normal, the return of variability reflected the subsequent state of neuronal function. Subsequent investigators have employed power spectral analysis techniques to study HRV in the setting of brain injury. Goldstein et al. observed that autonomic control of HR was disrupted in proportion to the degree of neurologic injury present in a population of pediatric patients with acute brain injury. Neurologic recovery from acute brain injury is associated with the restoration of normal HRV. The extinction of autonomic influence on HRV seen in brain death has been characterized in multiple studies. The potential of HRV analysis to predict outcome in the setting of severe TBI is an exciting possibility that has been explored by multiple investigators.

Several authors have identified a hyperadrenergic state in patients with severe TBI, as well as nontraumatic subarachnoid hemorrhage. Pulmonary dysfunction (e.g., neurogenic pulmonary edema, acute lung injury), immunosuppression (from increase in release of interleukin-10, inhibition of macrophage responsiveness to cytokines), and protein-calorie malnutrition (as a result of increased energy expenditure and protein catabolism) have all been correlated with and attributed to the hyperadrenergic state seen with severe TBI.

By investigating and treating the extracranial manifestations of severe TBI, these previously overlooked and harmful secondary insults become potential avenues for improving survival. Consistent with this, several authors have evaluated the impact of attenuating the hyperadrenergic state on outcome in patients with both traumatic and nontraumatic intracranial hemorrhage. Two randomized, controlled trials from the 1980s noted a decrease in intensity and duration of the hyperadrenergic state in patients treated with propranolol. However, these studies were small and did not evaluate the impact on mortality. Neil-Dwyer and colleagues demonstrated improved neurologic recovery and less cardiac and respiratory complications in patients with subarachnoid hemorrhage who received propranolol. Although not statistically significant (and not powered for such), there was a trend toward improved survival in those treated with βBs (p = 0.09). Other randomized controlled trials have noted a reduction in the incidence of myocardial infarction when these patients are treated with βBs. We recently evaluated the impact of exposure to βBs on mortality in patients with severe TBI. All patients who survived more than 3 days and had a head AIS score of 3 or greater were included. Exposure to βBs was associated with a significant reduction in mortality, with an adjusted relative risk of 0.29. This reduction in mortality was even more surprising when considering that those exposed to βBs were older, more
severely injured, had higher concomitant respiratory and infectious complications, and lower predicted survival by Trauma and Injury Severity Scoring. In the present study, we examined the impact of such interventions during the earlier phases of TBI resuscitation (first 24 hours) and among those with much more severe injuries (head AIS score ≥5) than those evaluated by our previous study. Again, βB exposure was associated with a reduction in mortality.

The influence of βBs on HRV in the TBI population remains to be fully characterized. Lampert et al.62 examined the effects of propanolol on recovery of HRV after acute myocardial infarction and noted that propanolol was associated with recovery of parasympathetic tone, which correlated with improved outcome. They also noted a decrease in the morning sympathetic predominance, suggesting a possible mechanism by which βBs decrease mortality and the risk of early-morning sudden death after myocardial infarction. Su et al. have recently investigated autonomic function in patients with varying degrees of brain injury; they noted augmented sympathetic and diminished parasympathetic drive related to the severity of brain stem damage.38 Taken together, these studies suggest a possible mechanism for the protective effects of βBs that we have observed in this study.

The current study is a large population-based investigation that was performed in an attempt to identify whether HRV could serve as a measure of TBI severity and to determine whether βBs could improve survival in this most severely injured population of patients (AIS score ≥5). We were able to successfully incorporate HRV as a means of stratifying patients based on severity of injury. In addition, we noted that exposure to βBs appeared to have the most impact on those whose initial 24-hour uncoupling exceeded 5%. Although insufficiently powered to demonstrate a statistically significant survival benefit, exposure to βBs appeared to “level the playing field” among the two populations. The finding that the mortality reduction is only a “trend”, should not detract from the results as those receiving βBs were older and more severely injured. Historically, these patients would be predicted to have a considerably higher mortality when compared with a younger, less injured cohort of patients (who did not receive βBs). Despite being one of the largest studies of severe TBI in the literature, this study was insufficiently powered to validate our hypothesis. Retrospective studies of drug efficacy are complicated by potential selection bias because of varying lengths of stay and indications for drug administration. These limitations should be addressed by a multi-institutional prospective, randomized trial of βB use in TBI. Such a trial should define subpopulations most likely to benefit, optimal timing of administration, particular agent (selective versus nonselective), and specific titration points.

Early cardiac uncoupling (reduction in HRV) in patients with severe TBI has been shown by several studies to be associated with a marked increase in mortality.1–5 In addition to supporting these findings, the current study also showed that the percentage of time spent in such an “uncoupled” state allowed stratification of mortality risk. Several authors have recently described an increase in survival in patients with TBI who were exposed to βBs.15,63 We noted that in the most severe forms of TBI (AIS score ≥5) βB exposure was associated with improved survival. Although this benefit lost statistical significance when those dying in the first 24 hours were excluded, the βB population was older and more severely injured. This group would have been expected to have a higher mortality when compared with a younger, less injured cohort not exposed to βBs. In addition, cardiac uncoupling identifies patients with severe TBI who are more likely to benefit from βB therapy. The present study further supports a call for a multi-institutional, randomized trial to investigate the effect of βBs on survival in patients with severe TBI, as well as identifying those most likely to benefit and therapeutic endpoints for these medications.

REFERENCES


The efficacy for propranolol in the prophylaxis of migraine headaches and essential tremor may be associated with β-2 receptors in the brain. Propranolol has also been shown to attenuate sympathetic activity in brain vasomotor centers.

We need to know what effect β-blockade will have on intracranial pressure and cerebral profusion pressure. We need to know how many patients exposed to β-blockers had a significant episode of hypotension and risk of secondary brain injury. It would be interesting to know the neurologic outcome in those survivors.

Our armamentarium of agents that may reduce cerebral metabolic oxygen demand is currently limited to sedative and analgesic agents. I think it is intriguing to imagine that β-blockers may one day be considered both a cardioprotective and cerebral-protective agent, but much more study needs to be done.

It’s time for the authors, as they say, to embark on a prospective study to validate their important findings relating cardiac uncoupling and mortality and to elucidate the potential role of β-blocker therapy in traumatic brain injury.

I only have one question that I would like Dr. Riordon to address at this time. Can you please speculate on the mechanism of action in which β-blockers may affect cardiac uncoupling and how this mechanism would confer a survival advantage in traumatic brain injury?

Dr. William P. Riordan (Nashville, Tennessee): The question of mechanism of action or potential mechanism of action for β-blockers in traumatic brain injury is a very interesting one.

I think there are several possible explanations for this and one of the very interesting things about this area of study is that reviewing the literature that’s out there in other fields, including heart failure, the cardiology literature, even neurology and pediatrics, is helpful to postulate.

I think the work that Lampert published on the β-blocker heart attack trials suggest one possible mechanism and that’s an alteration of the ratio of sympathetic to parasympathetic balance that helps contribute to your heart rate control from a central nervous system standpoint.

The other interesting thing to think about is what if it’s not blockade of beta receptors that we need, but boosting of parasympathetic drive through muscarinic agonists and so on. A lot of interesting work is being done in that area in Alzheimer literature.

I don’t have a good answer, one specific answer, for a potential mechanism, but I think it’s going to have to do with the balance of sympathetic and parasympathetic tone.

The other thing to think about is the sort of Lund approach to management of head injury, which involves consideration of cerebral volume regulation, and perhaps improvement of perfusion in areas of the brain that are injured.

Dr. Donald Jenkins (San Antonio, Texas): I have one question. What we always say in the intensive care unit is that being on a β-blocker doesn’t mean you’re beta blocked. Do
you have any data as far as the average heart rate of the patients? You may reach significance by using a heart rate goal to really show true β-blockade, as opposed to just being on a β-blocker.

**Dr. William P. Riordan:** We did not specifically look at whether we achieved β-blockade or achieved a certain target minimum heart rate. In fact, the way our analysis was done, a patient could have received a one-time β-blocker for hypertension and the reason that we, at least in this initial analysis, thought that would be appropriate is that if we’re postulating that β-blockers are helpful, if anything, that would sort of poison the rest of the data, because you never achieve β-blockade. You’re just adding another patient that was essentially minimally β-blocked, but I think your point is well taken, that that definitely needs to be considered in not only further retrospective studies, but in a prospective analysis.

**Dr. Sven Zenker** (Pittsburgh, Pennsylvania): I have two questions, the first one considering the type of data you acquire and what measure of ability did you use, I assume probably standard deviation or some other time to mean measure, and if so, what interval did you determine this?

The second being that the patients in systemic shock states are probably less likely to actually get β-blockers in the intensive care unit and have you tried to control for things like presser and inotropic use? I ask because patients in systemic shock states, I would imagine, would have worse outcomes in general.

**Dr. William P. Riordan:** The first question was regarding how do we acquire and essentially analyze the heart rate variability information, and there’s a number of different ways to do that.

Our system basically continuously samples the monitors in the unit and every 1 to 4 seconds records the heart rate. It’s not a regular sampling and so it has to be handled a little bit differently. What we do with that information is divide a 24-hour period into 5-minute increments.

In each 5-minute increment, we calculate a standard deviation of a heart rate and the previous work that we’ve done in this area shows a critically low range of that standard deviation of heart rate for a 5-minute interval to be a risk factor for poor outcome and that’s our measure of cardiac uncoupling.

We look at all the 5-minute ranges in a 24-hour period to yield a percentage of cardiac uncoupling and so if we say 5% uncoupled, that means that in the 24-hour period, the patient spends 5% of their time with their heart rate in that critically low range.

Previous investigators have used power spectral analysis techniques and in other words, sort of flipping from the time domain to the frequency domain using transform techniques that basically allow you to look at the spectrum of heart rate variability in hertz. You do get a little bit more information from those techniques, but it’s not as practical, I think, to collect and process real-time information from.

The second question was related to patients in shock and essentially their ability to tolerate a β-blocker and influence on that, in terms of indication and that’s another good point. It does seem that if somebody is admitted to the trauma intensive care unit and remains hemodynamically unstable, then they’re not even going to be considered for a β-blocker and that is part of the problem of analyzing drug efficacy like this, in a retrospective fashion.

**Dr. Edward Kelly** (Boston, Massachusetts): Have you considered the hypothesis that the β-blocking medicine is having an effect that’s irrelevant to the heart or the circulatory system, considering that we made no effort in the study to have a state of β-blockade defined by whatever heart rate or blood pressure you wanted and considering that previous studies in the intensive care unit have used a fixed dose of, say, atenolol to produce just the dose effect and not targeting to any physiologic effect, but yet there was still mortality benefit in nonselected general surgery patients?

**Dr. William P. Riordan:** I think that we may find that it’s not a heart rate or even a heart rate variability-dependent mechanism, but I think, as some of the other commenters have suggested, we really need to look at all aspects of this and the heart rate and heart rate variability is one area where we have a platform in place to continuously collect this information.

We know that heart rate variability is predictive of poor outcome, but that doesn’t mean that if we fix the heart rate variability that the patients are going to do well. We may find that we can give them a muscarinic agonist or a beta blocker or we can improve the heart rate variability or even return it to normal and they still have a poor neurologic outcome. I think that will become clearer in the next several years.

**Dr. Babak Sarani** (Philadelphia, Pennsylvania): Did you look to see if there were any differences in the brain itself between your groups of survivors and nonsurvivors? I assume all these patients had some form of intracranial pressure monitoring and so was there a difference in intracranial pressure, cerebral perfusion pressure (CPP), or if you measured brain tissue oxygen partial pressure (PbO2)?

**Dr. William P. Riordan:** That’s a good question and in this particular study, we did not look at intracranial pressure or any others. Intracranial pressure or CPP essentially are the two measures that we could have potentially looked at. This was intended to be more of an outcome type study, but that also would be important to look at.
Prehospital Loss of R-to-R Interval Complexity is Associated With Mortality in Trauma Patients

Andriy I. Batchinsky, MD, Leopoldo C. Cancio, MD, Jose Salinas, PhD, Tom Kuusela, PhD, William H. Cooke, PhD, Jing Jing Wang, MS, Marla Boehme, BS, Victor A. Convertino, PhD, and John B. Holcomb, MD

Background: To improve our ability to identify physiologic deterioration caused by critical injury, we applied nonlinear analysis to the R-to-R interval (RRI) of the electrocardiogram of prehospital trauma patients.

Methods: Ectopy-free, 800-beat sections of electrocardiogram from 31 patients were identified. Twenty patients survived (S) and 11 died (NonS) after hospital admission. Demographic data, heart rate, blood pressure, field Glasgow Coma Scale (GCS) score, and survival times were recorded. RRI complexity was assessed via nonlinear statistics, which quantify entropy or fractal properties.

Results: Age and field heart rate and blood pressure were not different between groups. Mean survival time (NonS) was 129 hours ± 62 hours. NonS had a lower GCS score (8.6 ± 1.7 vs. 13.2 ± 0.8, p < 0.05). RRI approximate entropy (ApEn; 0.87 ± 0.06 vs. 1.09 ± 0.07, p < 0.01), sample entropy (SampEn; 0.80 ± 0.08 vs. 1.10 ± 0.05, p < 0.01) and fractal dimension by dispersion analysis (1.08 ± 0.02 vs. 1.13 ± 0.01, p < 0.05) were lower in NonS. Distribution of symbol 2 (Dis_2), a symbol-dynamics measure of RRI distribution, was higher in NonS (292.6 ± 34.4 vs. 222 ± 21.3, p < 0.10). For RRI data, logistic regression analysis revealed ApEn and Dis_2 as independent predictors of mortality (area under the receiver-operating characteristic curve = 0.96). When GCSMOTOR was considered, it replaced Dis_2 whereas ApEn was retained (area under curve = 0.92). When Injury Severity Score was considered, it replaced GCSMOTOR; ApEn was retained.

Conclusions: Prehospital loss of RRI complexity, as evidenced by decreased entropy, was associated with mortality in trauma patients independent of GCS score or Injury Severity Score.

Key Words: Trauma, Prehospital, Mortality, Electrocardiography, Complexity, Nonlinear analysis, Spectrum analysis.

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To generate new, more informative vital signs, analysis of the electrocardiogram (ECG) has been pursued using a variety of techniques. One of these techniques (spectral analysis) measures the strength of periodic oscillations in the heart rate. Heart-rate variability (HRV), that is, variability in the length of the R-to-R interval (RRI) of the ECG, is affected by autonomic nervous system activity.2–4 RRI oscillations in the high-frequency range (those occurring at the respiratory rate, known as respiratory sinus arrhythmia) reflect vagal heart-rate control. RRI oscillations at the low-frequency range (about once every 10 seconds) reflect both vagal and sympathetic control of the heart rate. By taking the ratio of the low-frequency-to-high-frequency powers of these oscillations, a measure of the balance between sympathetic and vagal cardiac activities can be obtained (“sympathovagal balance”).3 As one would expect, hypovolemia has been shown to cause a compensatory increase in sympathovagal balance.5–7 On the other hand, sympathetic failure, manifested by a decrease in sympathovagal balance, was predictive of death in intensive care unit patients8,9 and in prehospital trauma patients.10,11

Rather than measure the strength of the periodic oscillations in the heart rate, an alternative approach to analysis of RRI variability measures the amount of irregularity, or complexity, in the heart rate. This irregularity is the result of the intricate and multilayered control mechanisms that fine-tune the heart rate.12 Complexity is a feature of normal cardiovascular regulation, whereas loss of complexity or “decomplexi-
fication” of the RRI has been shown in several studies to be a feature of disease and of impaired adaptation to physiologic stress. In this article, we use the term “complexity analysis” to refer to a family of tools more properly termed nonlinear statistics. Nonlinear behavior is the rule in biology. Biologic processes cannot be described by analysis of the simple sums of component variables, but involve products and powers of these constantly interacting variables. In the cardiovascular system, one consequence of this nonlinearity is the complex irregularity of the RRI. Nonlinear statistics are well suited for analysis of such signals.

We previously found in two animal models of hemorrhagic shock that RRI complexity, as measured by the Approximate Entropy technique, decreases during shock and is restored by fluid resuscitation. Similarly, others documented a decrease in the complexity of the RRI in human volunteers subjected to central hypovolemia by means of lower body negative pressure. The objective of the present study was to evaluate the ability of several such methods to discriminate between survivors and nonsurvivors of trauma in the prehospital setting. We hypothesized that loss of RRI complexity is associated with mortality after trauma.

**MATERIALS AND METHODS**

The Institutional Review Boards of the University of Texas Health Science Center, Houston, TX, and Brooke Army Medical Center, Fort Sam Houston, TX approved this study.

Patients were identified for this study using the Trauma Vitals database developed by the US Army Institute of Surgical Research (Fort Sam Houston, TX). The database stores prehospital patient data from point of injury until delivery via Life Flight helicopter to Memorial Hermann Hospital, a regional Level I trauma center in Houston, TX.

A ProPaq 206EL vital signs monitor (Welch-Allyn, Skaneateles Falls, NY) and a standard run sheet were used for data collection. Continuous ECG waveforms were collected with an iPAQ (Talla-tech RPDA, Tallahassee, FL) personal digital assistant interfaced to the monitor, and were recorded at a sampling frequency of 182 Hz. Vital signs, mechanism of injury (MOI, blunt or penetrating), field Glasgow Coma Scale (GCS) score, Abbreviated Injury Scores, Injury Severity Score (ISS), age, sex, and demographics were recorded. Blood pressures were measured automatically by cuff using the vital signs monitor. Blood pressures presented in this report were taken from the time point closest to the ECG segment extracted for analysis.

**Patient Selection**

The available data (117 patients recorded using the ProPaq 206EL vital signs monitor) were screened for presence of ECG recordings free of electromechanical noise (severe enough to prevent R-wave identification), free of ectopic beats, and at least 800 heart beats in length. Thirty-one patients with ectopy-free ECG waveforms were selected according to the above criteria from the 117 candidates available. Eighty-six patients were excluded because of multiple ectopic beats in the time series (S = 34, NonS = 13); electromechanical noise (S = 10, NonS = 22); or inadequate data length (S = 5, NonS = 2).

**ECG Analysis**

Eight-hundred-beat data sets from each subject were imported into WinCPRS software (Absolute Aliens Oy, Turku, Finland) and analyzed as a single discrete dataset as previously described. Eight-hundred beats were selected because HRV statistics are affected by the number of data points. Automatic identification of R waves was performed by the software, and manually verified in every data set. The software generated the instantaneous RRI time series.

The following are the main variables that were calculated:

**Time-Domain Analyses**

1. Mean RRI: the mean of the RRI, measured in milliseconds.
2. RMSSD: the square root of the mean of the sum of the squares of differences between consecutive RRIs.
3. pNN50: percentage of intervals that vary more than 50 ms from the previous interval.

**Spectral Analysis (Fast Fourier Transform)**

1. Low-frequency component of the RRI power spectrum, or low-frequency (LF) power: influenced by both sympathetic and vagal activity.
2. High-frequency (HF) power: influenced by vagal activity.
3. LF/HR and HF/HR ratios: reflect sympathovagal balance.
4. Total power: reflects the strength of oscillations throughout the entire power spectrum.
5. The LF, HF, and LF/HF ratio were normalized by dividing the LF and HF spectra by the total power. This yielded normalized powers (LFn/HFn) and their ratios (LFnu/HFnu, HFnu/LFnu).

**Spectral Analysis (Complex Demodulation)**

The method of complex demodulation (CDM) provides continuous assessment of the amplitude of high- and low-frequency fluctuations in the RRI.

1. CDM LF: a measure of the amplitude of the low-frequency fluctuations in the RRI.
2. CDM HF: a measure of the amplitude of the high-frequency fluctuations in the RRI.

**Complexity Analysis (Nonlinear Statistics)**

1. Approximate entropy (ApEn) and sample entropy (SampEn): measure the amount of irregularity in the RRI signal.
2. Fractal dimension by dispersion analysis (FDDA) and fractal dimension by curve lengths (FDCL): determine the fractal organization of the signal.
3. Detrended fluctuations analysis (DFA): determines fractal-like correlation properties and uncovers short- and long-range correlations within the signal.  
4. Similarity of distributions (SOD): explores the probability of similar RRI signal-amplitude distributions as a function of time.  
5. Signal stationarity (StatAv): assesses whether the mean and SD of the signal change during time during each data set.  
6. Symbol dynamics indices: symbol dynamics entropy (SymDyn), percentage of forbidden words (FW), and normalized symbol dynamics entropy (DisnEn) collectively measure the probability of certain patterns within the RRI time series.

**Statistical Analysis**

SAS version 8.1 (SAS Institute, Cary, NC) was used. Univariate analysis was performed using two-sample Student’s t test or Wilcoxon’s ranked sum test as appropriate for continuous variables, and the Cochran-Mantel-Haenszel statistic for score variables. In addition, correlation coefficients were calculated to determine relationships between continuous variables (Pearson correlation) and between dichotomous and continuous variables (point-biserial correlation). Spearman correlations were calculated between ordinal and continuous variables.

Multiple logistic regressions with stepwise selection and likelihood ratio tests were performed to identify independent predictors of mortality. Candidate variables were ECG-derived metrics as well as the motor component of the field GCS (GCS\textsubscript{MOTOR}) and the ISS. In the construction of logistic regression models to predict mortality, we considered this to represent a diagnostic problem with three overlapping phases. In the first phase (“remote triage”), only data derived from the RRI, and thus potentially available by remote telemetry, were considered. In the second phase (“prehospital care”), additional data available during hospitalization, including the ISS, were also considered.

We chose variables with a \( p \) value of <0.2 by univariate analysis as candidates for the logistic models. The Hosmer-Lemeshow goodness-of-fit test was used to estimate the regression model fit. A receiver-operating characteristic curve was constructed to assess the diagnostic performance of predictive equations. Estimated odds ratios and their 95% confidence intervals (CIs) were determined by the maximum likelihood method. The change in the Pearson \( \chi^2 \) statistic caused by deleting an individual observation was used to detect ill-fitted observations or outliers. If the model excluding outliers and influential cases had a classification accuracy rate that was better than the baseline model, which included all cases, the revised model was used. If the accuracy rate of the revised model without outliers and influential cases was less than 2\% more accurate, the baseline model was retained.

**RESULTS**

Age and hemodynamic data, to include the heart rate, were not statistically different between nonsurvivors (NonS) and survivors (S) (Table 1). Male gender and blunt mechanism of injury were relatively more common in the S group than in the NonS group. NonS were more severely injured and had a significantly lower GCS\textsubscript{TOTAL} and GCS\textsubscript{MOTOR}, and a higher ISS and Abbreviated Injury Score for the head (Table 1). Mean survival time (NonS) was 129 hours \( \pm 62 \) hours.

Time-domain and spectral analysis results are shown in Table 2. CDM revealed the amplitude of the LF oscillations of the RRI (significantly) and the HF oscillations of the RRI (not significantly) to be lower in NonS (Table 2). We additionally observed the following trends (not significant). NonS had lower nonnormalized HF and higher HF\textsubscript{nu} than the S group. The LF, LF\textsubscript{nu}, as well as LF/HF and LF\textsubscript{nu}/HF\textsubscript{nu} ratios were lower in NonS.

Complexity measures (obtained by nonlinear statistics) (Table 3), to include ApEn, SampEn, FDDA and the short-term scaling exponent by DFA were statistically \( (p < 0.05) \) lower in NonS than in S. Lower FDCL, Lempel-Ziv entropy (LZEn), and spectral entropy (SpEn) in NonS were not statistically distinguishable from S (data not shown). SOD was higher in NonS. StatAv was not different between the groups (Table 3).

Distribution of symbol 6 (Dis\textsubscript{6}), a symbol dynamics measure of RRI complexity, was lower in NonS (273.55 \( \pm \) 27.99 vs. 336.60 \( \pm \) 16.54, \( p < 0.05 \)). Distribution of symbol 2 (Dis\textsubscript{2}), was higher in NonS (292.6 \( \pm \) 34.4 vs. 222 \( \pm \) 21.3, \( p = 0.08 \)). Other symbol distributions were not different between groups.

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**Table 1 Demographics, Conventional Vital Signs, and Injury Scores**

<table>
<thead>
<tr>
<th>Variable</th>
<th>NonS</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>43.36 ( \pm ) 5.79</td>
<td>38.10 ( \pm ) 3.40</td>
</tr>
<tr>
<td>Sex</td>
<td>M (7), F (4)</td>
<td>M (15), F (5)</td>
</tr>
<tr>
<td>MOI</td>
<td>B (6), P (5)</td>
<td>B (13), P (7)</td>
</tr>
<tr>
<td>HR</td>
<td>117.46 ( \pm ) 8.54</td>
<td>99.63 ( \pm ) 4.39</td>
</tr>
<tr>
<td>MAP</td>
<td>74.62 ( \pm ) 9.54</td>
<td>82.7 ( \pm ) 4.84</td>
</tr>
<tr>
<td>GCS\textsubscript{TOTAL}</td>
<td>8.64 ( \pm ) 1.70(^*)</td>
<td>13.17 ( \pm ) 0.82</td>
</tr>
<tr>
<td>GCS\textsubscript{MOTOR}</td>
<td>3.36 ( \pm ) 0.72(^†)</td>
<td>5.50 ( \pm ) 0.32</td>
</tr>
<tr>
<td>AIS\textsubscript{HEAD}</td>
<td>3.00 ( \pm ) 0.73(^*)</td>
<td>0.70 ( \pm ) 0.34</td>
</tr>
<tr>
<td>ISS</td>
<td>36.55 ( \pm ) 2.90(^‡)</td>
<td>12.40 ( \pm ) 1.97</td>
</tr>
</tbody>
</table>

Data are means \( \pm \) SEM.  
\(^*\) \( p < 0.05 \)  
\(^†\) \( p < 0.01 \)  
\(^‡\) \( p < 0.001 \)

NonS, nonsurvivors; S, survivors; MOI, mechanism of injury; B, blunt; P, penetrating; MAP, mean arterial pressure; HR, heart rate; GCS\textsubscript{TOTAL}, field Glasgow Coma Score total; GCS\textsubscript{MOTOR}, field Glasgow Coma Score motor; AIS\textsubscript{HEAD}, Abbreviated Injury Score for the head; ISS, Injury Severity Score.
Table 2 Time- and Frequency-Domain Analysis Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>NonS</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRI</td>
<td>543.91 ± 47.37</td>
<td>626.30 ± 29.47</td>
</tr>
<tr>
<td>RMSSD</td>
<td>8.09 ± 2.16</td>
<td>11.60 ± 1.99</td>
</tr>
<tr>
<td>pNN50</td>
<td>0.38 ± 0.36</td>
<td>1.22 ± 0.99</td>
</tr>
<tr>
<td>TP</td>
<td>1673 ± 1325</td>
<td>576.35 ± 151.55</td>
</tr>
<tr>
<td>LF</td>
<td>174.64 ± 75.12</td>
<td>233.00 ± 62.22</td>
</tr>
<tr>
<td>HF</td>
<td>44.45 ± 17.83</td>
<td>73.05 ± 26.03</td>
</tr>
<tr>
<td>LF/HF</td>
<td>481.01 ± 201.53</td>
<td>558.12 ± 175.65</td>
</tr>
<tr>
<td>HF/LF</td>
<td>0.73 ± 0.23</td>
<td>0.34 ± 0.05</td>
</tr>
<tr>
<td>LFnu</td>
<td>0.57 ± 0.9</td>
<td>0.74 ± 0.03</td>
</tr>
<tr>
<td>HFnu</td>
<td>0.29 ± 0.05</td>
<td>0.22 ± 0.02</td>
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<tr>
<td>LFnu/HFnu</td>
<td>4.81 ± 2.01</td>
<td>5.55 ± 1.73</td>
</tr>
<tr>
<td>HFnu/LFnu</td>
<td>0.67 ± 0.20</td>
<td>0.33 ± 0.04</td>
</tr>
<tr>
<td>CDM LF</td>
<td>9.09 ± 4.15†</td>
<td>13.10 ± 2.11</td>
</tr>
<tr>
<td>CDM HF</td>
<td>3.27 ± 1.05</td>
<td>6.15 ± 1.24</td>
</tr>
</tbody>
</table>

Data are means ± SEM.
* p < 0.05.
† NonS, non-survivors; S, survivors; RRI, mean R-to-R interval of the ECG; RMSSD, root mean square standard deviation; pNN50, percentage of R-R intervals that vary by at least 50 ms; TP, total ECG; RMSSD, root mean square standard deviation; pNN50, percentage of R-R intervals that vary by at least 50 ms; TP, total ECG; LF, amplitude of the LF oscillations; CDM LF, amplitude of the LF oscillations; CDM HF, amplitude of the HF oscillations.

Table 3 Nonlinear Analysis Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>NonS</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApEn</td>
<td>0.87 ± 0.06*</td>
<td>1.09 ± 0.04</td>
</tr>
<tr>
<td>SampEn</td>
<td>0.80 ± 0.08*</td>
<td>1.10 ± 0.05</td>
</tr>
<tr>
<td>FDDA</td>
<td>1.08 ± 0.02†</td>
<td>1.13 ± 0.01</td>
</tr>
<tr>
<td>DFA</td>
<td>0.93 ± 0.14†</td>
<td>1.26 ± 0.08</td>
</tr>
<tr>
<td>SOD</td>
<td>0.28 ± 0.04†</td>
<td>0.19 ± 0.02</td>
</tr>
<tr>
<td>StatAv</td>
<td>0.89 ± 0.05</td>
<td>0.82 ± 0.03</td>
</tr>
<tr>
<td>FW (%)</td>
<td>51.45 ± 4.91</td>
<td>52.55 ± 2.28</td>
</tr>
<tr>
<td>DisnEn</td>
<td>0.62 ± 0.04</td>
<td>0.65 ± 0.02</td>
</tr>
</tbody>
</table>

Data are means ± SEM.
* p < 0.01.
† p < 0.05.
ApEn, approximate entropy; SampEn, sample entropy; FDDA, fractal dimension by dispersion analysis; DFA, detrended fluctuations analysis; SOD, similarity of distributions; StatAv, stationarity; FW, percentage of forbidden words; DisnEn, normalized symbol-dynamics entropy.

Association With Mortality

As explained above, construction of logistic regression models for prediction of mortality progressed through three phases. For the remote triage phase, RRI data were considered. ApEn and SampEn were highly correlated with each other (r = 0.99), and we selected ApEn for inclusion into our predictive models. Out of all the ECG-calculated variables, two independent predictors of mortality were identified: ApEn and Dis_2. The predictive model based on these variables produced the following equation:

\[ P(\text{mortality}) = e^{k(1 - \text{ApEn})} + 0.0092 \times (\text{Dis}_2). \]

The area under the receiver-operating characteristic curve (AUC) = 0.86 (95% CI = 0.71–1.0). After exclusion of outliers (1 case in NonS and 2 in S) the revised model improved:

\[ P(\text{mortality}) = e^{k(1 - \text{ApEn})} + 0.02 \times (\text{Dis}_2). \]

AUC = 0.956, (95% CI = 0.86–1.0; Fig. 1).

For the second or prehospital care phase, GCSMOTOR was added to the model yielding:

\[ P(\text{mortality}) = e^{k(1 - \text{ApEn})} + 0.01 \times (\text{Dis}_2) - 0.41 \times (\text{GCSMOTOR}). \]

AUC = 0.886 (95% CI = 0.75–1.0). After exclusion of outliers (1 case in group S) Dis_2 was excluded from the model, whereas ApEn was retained:

\[ P(\text{mortality}) = e^{k(1 - \text{ApEn})} + 0.02 \times (\text{Dis}_2). \]

AUC = 0.956, (95% CI = 0.86–1.0; Fig. 2).

Upon consideration of the ISS for the third or definitive care phase, it replaced the GCSMOTOR in the model, whereas ApEn was again retained:

\[ P(\text{mortality}) = e^{k(1 - \text{ApEn})} + 0.08 \times (\text{GCSMOTOR}). \]

AUC = 0.92 (95% CI = 0.80–1.0; Fig. 2).

DISCUSSION

This report introduces the use of complexity analysis of the RRI for prediction of mortality in prehospital trauma patients. There were two principal findings: (1) prehospital loss of RRI complexity, as measured by several complementary but computationally different nonlinear metrics, characterized and separated nonsurvivors from survivors. (2) One measure of RRI complexity, ApEn, was an independent predictor of in-hospital mortality, even when variables such as field GCSMOTOR and ISS were taken into account. ApEn outperformed traditional vital signs, such as blood pressure and...
heart rate, which did not demonstrate statistically significant differences between nonsurvivors and survivors in this study.

**Complexity Analysis**

Physiologic processes such as the RRI display nonlinear responses to stimuli and feature complex, irregular patterns of variability. These complex patterns in the signal reflect input from multiple, interacting, feedback-controlled systems. We think that analysis of the complexity of the RRI with nonlinear methods allows assessment of the complexity, and thus the health, of the underlying system, which controls the heart rate.

Why does RRI complexity exist? Passage of information through nonlinear regulatory networks probably facilitates adaptability to stress, whereas loss of complexity may imply maladaptation and informational isolation of the system. This may explain why a system with higher complexity is associated with survival and is more error tolerant, whereas a system with low complexity and less variability is associated with disease or death. However, the precise mechanism(s) responsible for the observed changes in complexity with disease or shock remain to be deciphered.

One method of measuring RRI complexity quantifies the amount of irregularity, or entropy, in the signal. In our study, ApEn and SampEn were lower in nonsurvivors than in survivors. Palazzolo et al. documented a decrease in ApEn secondary to hypotension in dogs. Similarly, we showed decreased ApEn and SampEn during hemorrhagic shock in anesthetized swine. Hogue et al. identified that decreased entropy was an independent predictor of atrial fibrillation in patients after coronary artery bypass grafting. Decreased entropy was associated with myocardial ischemia, manifested by angina. Thus, decreases in RRI complexity as measured by entropy appear to be associated with physiologic deterioration in a variety of conditions.

Another method of measuring RRI complexity takes advantage of the fact that the normal RRI possesses fractal characteristics. This means that shorter sections of the RRI are structurally similar to longer sections, i.e. that the signal possesses “self-similarity” at both small and large scales. As measured by FDDA (significantly) and FDCL (nonsignificantly), NonS showed a loss of fractal structure. We have previously shown a decrease in FDDA during hemorrhagic shock in swine. West et al. found a decline in RRI fractal dimension in humans during central hypovolemia induced by lower body negative pressure. A breakdown in fractal properties may be an indicator of a more regular structural organization of the signal and solidifies our findings of lower complexity in the NonS group.

DFA is another method of measuring the self-similarity of fractal processes that quantifies the short- and long-term correlations within the data. In this study we assessed the scaling exponent reflecting the short-term correlations in the RRI signal and found it to be significantly lower in the NonS, denoting breakdown of correlations. In 24-hour Holter recordings of 446 survivors of myocardial infarction, Huikuri et al. found the DFA short-term exponent to be an independent predictor of death. Loss of RRI complexity measured by decreased short-term fractal scaling properties predicted mortality in survivors of acute myocardial infarction. Vikman et al. found that a decrease in RRI ApEn and short-term RRI...
dynamics (DFA) preceded the spontaneous onset of atrial fibrillation in patients with no structural heart disease, whereas traditional HRV metrics did not change.28 Our findings are therefore consistent with the literature indicating an association between loss of RRI fractal scaling and life-threatening disease.

SOD is a method that allows for rapid online analysis of small datasets, as it explores the probability of similar RRI signal amplitude distributions as a function of time.23 SOD was higher in NonS, reflecting greater regularity of signal distribution and thus a state of lower complexity among NonS.

The symbol-dynamic indices collectively measure the probability of certain patterns within the RRI time series.25 In our study, the FW and the normalized entropy of the symbol dynamics (DisnEn) were not different between the groups, possibly denoting low sensitivity of this method.32 In addition, we found that the average of pattern 6 of symbol words (Dis_6) was higher and pattern 2 (Dis_2) was lower in NonS, with the latter included into the “remote triage” predictive model. At this point, limited experience with these methods prevents us from drawing firm conclusions about the physiologic meaning of these specific patterns (Dis_6 and Dis_2), and application of the methods to larger data sets will be needed to place these findings in perspective.

Spectral Analysis

The method of CDM provides continuous assessment of the amplitude of high- and low-frequency fluctuations in the RRI, and is insensitive to data length and nonstationarity in the signal.19 As measured by CDM, the amplitude of LF and HF oscillations (the latter nonsignificantly) were both lower in NonS. These changes paralleled those seen in the standard nonnormalized frequency-domain metrics. Overall, these findings indicate inappropriately low sympathetic activity in the NonS group.

Previous work by Winchell and Hoyt on intensive care unit patients,9 as well as from our institution on prehospital trauma patients,10,11 identified lack of sympathetic tone and a state of decreased sympathovagal balance in NonS.9,10 Consistent with those reports, in this study the trends in the LF, LFnu, and LF/HF ratio were all numerically lower in the NonS group along with a higher HFnu, HF/LF ratio, and HFnu/LFnu ratio (Table 2). Lack of statistical significance in these observations likely reflects sample size, dataset length and, perhaps, the methodologic limitations of these methods.

Prediction of Mortality

The first predictive model explored in our study reflected the discriminative capacity of ECG-derived metrics alone, and modeled a scenario in which an ECG signal is analyzed remotely and before hands-on evaluation of the casualty (“remote triage” model). The respectable sensitivity and specificity (that further improved with elimination of outliers) underlines the potential utility of entropy measurements for remote prognosis and diagnosis. Inclusion of the GCSMOTOR in the second predictive model conceptualizes arrival of a medic to the casualty and a physical examination in addition to the ECG analysis (“prehospital care” model). Finally, in the third (“definitive care”) model, ApEn was retained and ISS was added as independent predictors of mortality. Thus, in this dataset ApEn possibly accounts for differences in the robustness of an individual’s response to injury, even when ISS is taken into account.

Limitations

The hemodynamic data (heart rate and mean arterial blood pressure) were numerically but not statistically different between S and NonS in this study. Thus, the possibility of a type II error exists in this small sample size. We investigated prehospital trauma patients with ECGs that did not contain prohibitive levels of mechanical noise or arrhythmias, and were 800 beats long. These limitations led us to the sample size of 31 of the original 117 as outlined in our patient inclusion criteria. It is possible that those trauma victims who are more critically ill, and therefore more likely to die, might have more noisy ECGs because of, for example, ongoing interventions during transport. Indeed, the mortality rate was 43% in the excluded group versus 35% in the included group. Otherwise, excluded patients did not differ from included patients with respect to the male-to-female ratio, age, mean arterial pressure, or ISS. Clearly, however, it would be premature to generalize our findings to other trauma patients. Efforts are ongoing to improve the quality of ECG results collected in the field, and to determine the absolute minimum dataset length (number of beats) needed for accurate patient classification. Reduction of dataset size would widen the utility of the proposed methods during short transport times.

The endpoint, in-hospital mortality, was chosen in our study for its unequivocal ability to categorize outcome. However, of greater importance to the prehospital provider is the ability to predict the need for a lifesaving intervention. Studies are ongoing to verify the utility of the methods explored here in prediction of lifesaving interventions.

The analysis methods used in this study require modest computing power and could be incorporated into microchips, personal digital assistants, or commercial monitors, making these tools readily available for clinical use. It is clear that there are several quite different ways to quantify what is generally called “heart-rate variability”, to include indices derived from spectral analysis (such as sympathovagal balance) and from complexity analysis (such as approximate entropy). Prospective, large-scale clinical trials will be needed to determine the clinical utility of these methods in guiding decision making, and to define the merits of these different approaches.

CONCLUSION

Loss of RRI complexity, as evidenced by decreased entropy, diminished fractal scaling, loss of short-term cor-
relations in the RRI, and higher similarity of distributions in the signal, characterized nonsurviving trauma patients and distinguished them from survivors. The fact that several computationally different methods pointed to loss of complexity in NonS lends additional weight to these findings. Prehospital loss of RRI complexity, measured by ApEn, was associated with mortality independent of the field GCS\textsubscript{MOTOR} and hospital ISS. Evaluation of cardiovascular complexity may be useful for noninvasive, remote triage.

ACKNOWLEDGMENTS

We thank Denise Hinds, RN for patient data collection.

REFERENCES

Use of Long-Term Anticoagulation is Associated With Traumatic Intracranial Hemorrhage and Subsequent Mortality in Elderly Patients Hospitalized After Falls: Analysis of the New York State Administrative Database

Fredric M. Pieracci, MD, MPH, Soumitra R. Eeachempati, MD, FACS, Jian Shou, MD, Lynn J. Hydo, MBA, and Philip S. Barie, MD, MBA, FCCM, FACS

Background: Previous studies addressing the relationship between anticoagulation and risk of traumatic intracranial hemorrhage (ICH) have provided conflicting results, and have examined infrequentlyelderly patients after falls. We used a statewide hospital discharge database to test the hypothesis that long-term anticoagulation (LTA) increases the likelihood of traumatic ICH and subsequent mortality in this patient population.

Methods: Patients aged 65 years or older and hospitalized as the result of a fall were extracted from the New York Statewide Planning and Cooperative Systems Database for the year 2004. LTA, ICH, and additional injuries including skull fracture, vertebral fracture, rib fracture, lower extremity fracture, thoracic visceral injury, and abdominal visceral injury were defined using corresponding International Classification for Disease, Ninth Edition coding. Covariates included age, gender, and comorbidity. Additional outcomes included length of stay and mortality. Multivariable logistic regression was used to identify independent predictors of traumatic ICH and subsequent mortality.

Results: A total of 47,717 patients met the inclusion criteria. Falls were associated with a traumatic ICH in 2,517 patients (5.1%), and the mortality rate of patients with a fall-related, traumatic ICH was 15.5% (n = 394). A total of 1,511 (3.2%) patients hospitalized after a fall used LTA. Based on univariate analysis, ICH was the only injury that occurred more commonly in patients who used LTA, when compared with those who did not (8.0% vs. 5.3%, respectively, \( p < 0.0001 \)). Furthermore, although overall mortality did not differ by use of LTA, mortality after ICH was significantly higher in patients who used LTA when compared with those who did not (21.9% vs. 15.2%, respectively, \( p = 0.04 \)). Controlling for age, gender, and comorbidity, patients on LTA were 50% more likely to sustain a traumatic ICH after a fall (odds ratio = 1.50; 95% confidence interval, 1.23–1.81; \( p < 0.0001 \)). Furthermore, among patients who sustained an ICH, mortality was 1.57-fold greater in patients on LTA (odds ratio = 1.57; 95% confidence interval, 1.02–2.45; \( p = 0.04 \)).

Conclusions: These data indicate that use of LTA is independently associated with traumatic ICH and subsequent mortality in elderly patients hospitalized after a fall.

Key Words: Anticoagulation, Intracranial hemorrhage, Traumatic brain injury, Geriatrics, Falls.


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Address for reprints: Fredric M. Pieracci, MD, MPH, Departments of Surgery and Public Health, Weill Medical College of Cornell University, 411 East 69th Street, KB-220, New York, NY 10021; email: frp9005@med.cornell.edu.
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Although the increased risk of both overall bleeding complications and spontaneous ICH has been well documented in patients who use LTA, the relationship between LTA and adverse outcomes after trauma is less clear. Studies that have investigated trauma patients both collectively and after orthopedic injury have failed to document increased morbidity and mortality in patients who use LTA. Furthermore, two recent studies that investigated specifically patients with head injuries did not observe an association between traumatic ICH and anticoagulation at the time of injury. Conversely, several single-institution studies, including data from our trauma center, have documented a significantly increased likelihood of ICH and subsequent mortality in the anticoagulated patient with head injuries.

To date, no study has examined this relationship specifically after falls among elderly patients. Restriction to this demographic is advantageous because it eliminates possible confounding by injury mechanism, which has obscured interpretation of previous findings. Furthermore, because a high risk of falling is a commonly cited contraindication to the initiation of LTA, documentation of an association between LTA and adverse outcomes after trauma is less clear. Studies that have investigated trauma patients both collectively and after orthopedic injury have failed to document the initiation of LTA, as indicated by the presence in any diagnostic field of at least one of the following ICD-9 codes: 800.2, 800.3, 800.7, 800.8, 801.2, 801.3, 801.7, 801.8, 803.2, 803.3, 803.7, 804.3, 804.7, 804.8, 852, or 853. These codes, which refer specifically to traumatic ICH, as opposed to spontaneous hemorrhage, have been validated previously. Additional injuries included skull fracture (800.00–804.99), vertebral fracture (805.00–806.9), rib fracture (807.00–807.19), pelvic fracture (808.0–808.9), long-bone fracture of the lower extremity (820.00–821.39, 823.00–823.92), thoracic visceral injury (860.0–862.9), and abdominal visceral injury (863.0–868.19). Additional outcomes included hospital length of stay (LOS), overall mortality, and mortality after traumatic ICH.

Covariates included age, gender, diagnosis of atrial fibrillation (427.31), and overall comorbidity, assessed using the Charlson comorbidity index adapted by Deyo et al. for use with administrative data. The Deyo comorbidity score assigns points based on the presence of 19 comorbid conditions, ranging from 1 to 6 for each condition, for a total possible score of 37.

All statistics were computed using SAS version 9.1 (SAS Institute, Cary, NC). Statistical significance was set at an alpha error level of 0.05. Student’s t test and \( \chi^2 \) test were used to evaluate differences in continuous and categorical variables, respectively. A multiple logistic regression model was fit using a forward selection method to evaluate the independent effects of LTA on the likelihood of binary outcomes. The overall contribution of the fitted model to predicting variability in the outcome variable was assessed using the likelihood ratio \( \chi^2 \) test. Model fit was assessed using the Hosmer-Lemeshow test. In the case of overall model significance, the independent contribution of individual variables was assessed using the Wald \( \chi^2 \) test and expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

### RESULTS

A total of 49,464 admissions related to falls occurred in elderly patients for the year 2004, comprising 6.0% of all hospitalizations in this age group. Of these patients, 1,747 (3.5%) were excluded because of congenital clotting factor abnormalities, thrombocytopenia, or underlying liver disease, leaving a final sample size of 47,717. Types of falls are shown Table 1. A total of 1,511 (3.2%) patients were on LTA. Additional sample characteristics, including associated injuries, are summarized in Table 2.

As shown in Table 3, there was no difference in age according to use of LTA, although patients who used LTA were more likely to be male \( (p < 0.0001) \). Deyo comorbidity scores were clinically similar between groups, although statistically different \( (p = 0.006) \). There was no difference in either hospital LOS or overall mortality according to use of LTA. The only injury that occurred with a significantly increased frequency in patients who used LTA, when compared with those who did not, was ICH \( (8.0\% \text{ vs. } 5.3\%, \text{ respectively}, \ p < 0.0001) \). Furthermore, patients who used LTA were significantly more likely to die after ICH when compared with patients who did not use LTA \( (21.9\% \text{ vs. } 15.2\%, \text{ respectively}, \ p = 0.04) \).
Multivariable logistic regression was performed to adjust for baseline differences in demographics according to use of LTA (Table 4). After controlling for age, degree of comorbidity, and gender, LTA patients remained significantly more likely to sustain an ICH (OR = 1.50; 95% CI, 1.23–1.81; \( p < 0.0001 \)) and die after ICH (OR = 1.57; 95% CI, 1.02–2.45; \( p = 0.04 \)).

To address further the issue of confounding, we performed a subgroup analysis of patients with atrial fibrillation (n = 8,421, 17.6%). By univariate analysis, use of LTA was associated strongly with a diagnosis of atrial fibrillation (OR = 9.73; 95% CI, 8.73–10.85; \( p < 0.0001 \)). However, only 984 patients (11.7%) with atrial fibrillation used LTA. Among patients with atrial fibrillation, LTA continued to be associated with ICH (OR = 1.26; 95% CI, 1.02–1.62; \( p = 0.04 \)). Furthermore, a trend was observed among patients with atrial fibrillation in the likelihood of subsequent mortality in LTA patients when compared with controls (OR = 1.36; 95% CI, 0.81–2.39; \( p = 0.19 \)).

**DISCUSSION**

This study represents the first to our knowledge to address the relationship between LTA and ICH specifically among elderly patients hospitalized as the result of a fall. In an analysis of all such admissions in New York State for the year 2004, we found that use of LTA was associated with a 50% increase in the likelihood of traumatic ICH, and a 57% increase in the likelihood of subsequent mortality. Among the injuries queried, only ICH occurred with a significantly increased frequency among patients using LTA, suggesting a specific association between these two parameters. Furthermore, although overall mortality did not vary by use of LTA, mortality after ICH was significantly increased in those patients who used LTA. These associations persisted in a subgroup analysis of patients with atrial fibrillation.
Numerous studies have addressed the relationship between preinjury anticoagulation (most commonly with warfarin) and outcomes after geriatric trauma. However, these studies have varied by inclusion criteria, outcomes, and findings. Both statewide \(^{20}\) and single-institution \(^{19,21}\) studies have failed to document an increased likelihood of adverse outcomes after trauma in anticoagulated patients, although these studies did not analyze specifically the likelihood of ICH. The comparable overall mortality, LOS, and associated injuries exclusive of ICH observed between LTA groups in the present study are consistent with these findings.

Investigations specific to the association between LTA and traumatic ICH have yielded mixed results. LTA with warfarin was not associated with an increased likelihood of traumatic ICH in either a sample of elderly Medicare beneficiaries with atrial fibrillation,\(^{8}\) or a single-institution’s trauma experience.\(^{22}\) However, Gage et al.\(^{8}\) used warfarin prescription at discharge from a prior hospitalization as a surrogate for warfarin use at the time of a subsequent hospitalization for ICH. Because discontinuation or initiation of anticoagulation in the interim was not captured, the true prevalence of anticoagulation use at the time of hospitalization was unknown. Mina et al.\(^{22}\) did not observe an association between preinjury warfarin use and ICH in a single-institution study that included all mechanisms of injury. However, although controls were matched to warfarin users by age, the former were significantly more likely to sustain head injury as the result of a motor vehicle collision. By contrast, the majority of warfarin users (91.5%) sustained head injury as the result of a fall. Accordingly, differences in injury kinetics may have confounded the observed increased prevalence of ICH in the control group. In contrast to these two studies, several recent reports of elderly patients with head injuries have noted an increased likelihood of traumatic ICH,\(^{23,26}\) severity of ICH,\(^{24,25}\) overall mortality,\(^{24,26}\) and mortality after ICH\(^{25,26}\) in anticoagulated patients when compared with other patients.

The present study adds to the literature supporting an association between LTA and traumatic ICH by documenting a specific relationship between these two parameters in a multi-institutional sample of elderly patients with similar mechanism of injury. Unlike the study by Gage et al.,\(^{8}\) use of LTA was captured at the time of hospitalization for trauma. Furthermore, statewide analysis eliminated biases that may result from single-institution studies, such as marked variations in the management of the anticoagulated patient with head injuries.\(^{26}\) Analysis of a large sample also affords statistical power sufficient to detect differences in outcomes, even after controlling for baseline disparities between LTA groups. The possible confounding by underlying variations in health status was also addressed through subgroup analysis of patients with atrial fibrillation. The persistent relationship between LTA and traumatic ICH in this subgroup strengthens the argument for an independent association. This analysis is also of clinical relevance because atrial fibrillation is by far the most common indication for LTA among elderly trauma patients.\(^{19,25}\) Finally, restriction of the patient sample to those hospitalized as the result of a fall minimized confounding by mechanism of injury.

Delineation of the relationship between LTA and traumatic ICH after falls is of clinical relevance because, beginning at age 65, falls comprise the most common mechanism of injury.\(^{3,22}\) Patients at high risk for falls have been excluded from randomized trials that evaluate the efficacy and safety of LTA, thus precluding prospective data collection.\(^{37}\) Despite this, physicians commonly withhold LTA from patients at high risk for falls.\(^{27-29}\) By contrast, a recent consensus statement concluded that major bleeding as a result of falls was not more common in patients using LTA.\(^{38}\) Furthermore, the American College of Chest Physicians does not include fall risk in the decision to initiate LTA.\(^{37}\) As this controversy persists, falls remain the most common mechanism of injury among LTA users.\(^{25}\)

The decision to initiate LTA, regardless of indication, involves a careful risk-benefit analysis conducted at the level of the individual patient. In the case of atrial fibrillation, the decreased risk of thromboembolic stroke\(^{39}\) is weighed against the increased risk of bleeding, including traumatic ICH. Man-So-Hing et al. performed a decision analysis in which the rates of both ICH and falls were varied in a hypothetical cohort of elderly patients with atrial fibrillation.\(^{1}\) In order for LTA with warfarin not to be the preferred treatment (measured using quality-adjusted life years), the relative risk of ICH when using warfarin when compared with no therapy would have had to exceed 29. Furthermore, the anticoag-

### Table 4 Results of Multivariable Logistic Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model I: ICH OR (95% CI)</th>
<th>p</th>
<th>Model II: Mortality After ICH OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00† (0.99–1.01)</td>
<td>0.43</td>
<td>1.04† (1.02–1.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Deyo comorbidity score</td>
<td>0.97§ (0.94–0.99)</td>
<td>0.04</td>
<td>0.99§ (0.91–1.09)</td>
<td>0.86</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.47 (0.43–0.51)</td>
<td>&lt;0.0001</td>
<td>0.61 (0.49–0.76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Long-term anticoagulation</td>
<td>1.50 (1.23–1.81)</td>
<td>&lt;0.0001</td>
<td>1.57 (1.02–2.45)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

† Refers to the increase in odds of the relevant outcome for a 1-year increase in age.
‡ Refers to the increase in odds of the relevant outcome for a one-point increase in comorbidity score.
§ Refers to the increase in odds of the relevant outcome for a one-point increase in comorbidity score.
lated patient would have had to fall nearly 300 times annually for warfarin not to be the preferred treatment.

Because LTA seems to be the optimal treatment strategy for patients with atrial fibrillation, as well as several additional conditions common among elderly patients, it is imperative that trauma centers both recognize the increased risk of ICH in patients who use LTA and implement measures to minimize associated morbidity. Evidence-based interventions range from preventive measures to implementation of standardized protocols for rapid evaluation of anticoagulated patients with head injuries, with subsequent reversal of anticoagulation. Despite improved outcomes realized with such protocols, only 12% of trauma centers have them in place.36

Use of administrative data introduces several limitations, most notably coding bias. In particular, use of V58.61 as a surrogate for LTA, although employed previously in the literature, has not been validated using chart abstraction. Furthermore, the prevalence of LTA among elderly patients in our sample was lower than that reported in recent retrospective case series.13,14 However, the reported prevalence of LTA in patients with atrial fibrillation varies markedly among studies. Johnston et al. reported that only 9.7% of patients with newly diagnosed atrial fibrillation filled prescriptions for warfarin within the study period.30 Moreover, a low prevalence of LTA in our sample may reflect a higher risk of fall (inclusion criteria specified patients who required hospitalization as the result of a fall) and thus reluctance to both prescribe and use LTA. Both surveys have demonstrated that health-care providers avoid prescription of LTA to patients with atrial fibrillation who are perceived as likely to fall.

Secondly, we were unable to capture the level of anticoagulation at the time of injury. This is of concern because as many as one-half of trauma patients using LTA are subtherapeutic at the time of presentation.26 However, pooling of therapeutic and subtherapeutic patients would underestimate the likelihood of traumatic ICH among patients using LTA. More generally, use of administrative data is unable to provide detailed information regarding mechanism of injury, acuity, or hospital course. Accordingly, injury severity scores, results from imaging studies (such as ICH size), and both frequency and rapidity anticoagulation reversal were unknown.

Third, because of the retrospective nature of our study, we are unable to prove a causal relationship between LTA and traumatic ICH after falls. Additional differences between patients who do and do not use LTA may contribute to the increased likelihood of traumatic ICH in the former group. Several reports have demonstrated an increased number of comorbid conditions in patients who use LTA.20,24 In the present study, this difference was clinically insignificant, and comorbidity was controlled for in the regression models. However, additional, unmeasured differences in health status may exist nonetheless. Although use of a cross-sectional study design also raises the possibility of reverse causality, it is unlikely that LTA would be initiated more frequently after ICH.

Fourth, our sample was restricted to patients who required hospitalization, thereby excluding patients who either did not seek medical attention or were not admitted as a result of falling. This limitation, which is pervasive in the aforementioned literature, reflects the inherent difficulty in capturing the true prevalence of falls and subsequent morbidity in the community.

In conclusion, this statewide investigation of elderly patients hospitalized after a fall documented an increased likelihood of both traumatic ICH and subsequent mortality in patients using LTA. Although our study is limited by the use of administrative data, the specificity of the relationship between LTA and ICH in a multi-institutional sample of patients after a similar injury mechanism provides evidence for an independent association between these two parameters. These findings, in addition to similar results from single-institution studies, should both inform individual patient-based decisions to initiate LTA, and motivate health-care providers to prepare effectively for the projected increase in number of anticoagulated patients with head injuries.

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Degree of Anticoagulation, but Not Warfarin Use Itself, Predicts Adverse Outcomes After Traumatic Brain Injury in Elderly Trauma Patients

Fredric M. Pieracci, MD, MPH, Soumitra R. Eachempati, MD, FACS, Jian Shou, MD, Lynn J. Hydo, MBA, and Philip S. Barie, MD, MBA, FCCM, FACS

Background: The relationship between preinjury warfarin use and outcomes after traumatic brain injury in elderly trauma patients remains controversial. We hypothesized that, among elderly warfarin users, the degree of anticoagulation, rather than warfarin therapy itself, would predict the severity of traumatic brain injury.

Methods: Retrospective study (2004–2006) of all elderly trauma patients (age ≥65 years) who were evaluated by the trauma service at a Level I trauma center and underwent computed tomography of the head for suspicion of an intracranial injury was performed. Three cohorts were grouped: (1) warfarin users with an admission International Normalized Ratio ≥2 (therapeutic group), (2) warfarin users with an admission International Normalized Ratio <2 (nontherapeutic group), and (3) warfarin nonusers. Main outcome variables were presenting with a Glasgow Coma Scale (GCS) score ≤13 points, intracranial hemorrhage (ICH), overall mortality, and mortality after ICH.

Results: A total of 225 trauma patients were studied, including 40 warfarin users (17.3%), of whom 22 (55.0%) were in the therapeutic group. Age, gender, and mechanism of injury were similar among groups. Likelihood of Glasgow Coma Scale score ≤13 (odds ratio [OR] = 5.13, 95% confidence interval [CI] 1.97–13.39, p = 0.001), ICH (OR = 2.59, 95% CI 0.92–7.32, p = 0.07), overall mortality (OR = 4.48, 95% CI 1.60–12.50, p = 0.004), and mortality after ICH (OR = 3.42, 95% CI 1.09–10.76, p = 0.03) was increased in the therapeutic as compared with the nonuser group. There was no difference in any measured outcome between the nonuser and nontherapeutic groups.

Conclusions: Therapeutic anticoagulation with warfarin, rather than warfarin use itself, is associated with adverse outcomes after traumatic brain injury in elderly patients.

Key Words: Warfarin, Intracranial hemorrhage, Traumatic brain injury, Geriatrics, Anticoagulation.

Intracranial hemorrhage (ICH) is a common sequela of traumatic brain injury in elderly trauma patients, which is associated with substantial morbidity and mortality.1 De-
increased risk of ICH and subsequent mortality; and (2) nontherapeutic warfarin users and nonusers are at similar risk for ICH and subsequent mortality.

PATIENTS AND METHODS

Medical records of all elderly (age ≥65 years) patients evaluated by the trauma service at a Level I trauma center from June 2004 to June 2006 were reviewed. Patients were included if they underwent computed tomography of the head (CTH) for suspicion of ICH. The main predictor variables were both warfarin use and degree of anticoagulation at the time of injury as measured by the INR. On the basis of this information, three groups were formed: (1) warfarin users with an admission INR ≥2 (therapeutic group), (2) warfarin users with an admission INR <2 (nontherapeutic group), and (3) warfarin nonusers. Patients who underwent initial management at another hospital were included only if the INR at the time of admission to that hospital was noted in the medical record. The primary outcome variable was the presence of ICH as documented by the final CTH report of an attending radiologist. Secondary outcomes included presenting Glasgow Coma Scale (GCS) score (dichotomized as >13 points or ≤13 points), overall mortality, and mortality after ICH.

All statistics were computed using SAS version 9.1 (SAS Institute, Cary, NC). Statistical significance was set at an α error level of 0.05. Differences in continuous variables among the three groups were compared using multigroup analysis of variance. When the analysis of variance test was significant at the 0.05 level, differences in means of continuous variables between individual groups were compared using the Mann-Whitney U test. Differences in categorical variables among the three groups were compared using the multigroup χ² test, unless expected cell counts were <5, in which case the Fishers exact test was used.

RESULTS

A total of 225 medical records were abstracted; 40 patients (17.8%) were warfarin users. Sample demographics are shown in Table 1. ICH was diagnosed in over one-half of patients who underwent CTH (n = 131, 58.2%). Overall mortality was 11.9% (n = 26), and 21 of the 26 patients who died (80.8%) had an ICH. As shown in Table 2, there were no significant differences between patients with and without an ICH with respect to age (p = 0.84), gender (p = 0.50), and preinjury use of clopidogrel (p = 0.28). A higher prevalence of preinjury aspirin use among patients with an ICH approached, but did not reach, statistical significance (p = 0.08). Mechanism of injury differed significantly between patients with and without an ICH (p = 0.02). Furthermore, as compared with patients without an ICH, patients with an ICH had a significantly increased mortality rate (5.4% vs. 16.5%, respectively, p = 0.01). Finally, nonsignificant trends were observed for an increased presenting INR (p = 0.06), a lower presenting GCS score (p = 0.15), and a higher prevalence of therapeutic warfarin users (p = 0.10) in patients with an ICH, as compared with those without an ICH.

Of the 40 patients who were warfarin users at the time of injury, 22 (55.0%) had an admission INR ≥2 (therapeutic group), and the remaining 18 patients (45.0%) constituted the nontherapeutic group. Atrial fibrillation was the most common indication for warfarin therapy (n = 28, 70.0%), followed by mechanical heart valve (n = 3, 7.5%), history of cerebrovascular injury (n = 3, 7.5%), unknown indication (n = 3, 7.5%), treatment of venous thromboembolic disease (n = 2, 5.0%), and venous thromboembolic disease prophylaxis (n = 1, 2.5%). Admission INR information was available for all patients.

Table 1 Sample Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (Range or %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>79.5 (65–101)</td>
</tr>
<tr>
<td>Male</td>
<td>94 (42.0)</td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>163 (72.4)</td>
</tr>
<tr>
<td>Pedestrian struck</td>
<td>44 (20.0)</td>
</tr>
<tr>
<td>Motor vehicle collision</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>12 (5.3)</td>
</tr>
<tr>
<td>Preinjury aspirin</td>
<td>74 (33.0)</td>
</tr>
<tr>
<td>Preinjury warfarin</td>
<td>40 (17.8)</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>22 (55.5)</td>
</tr>
<tr>
<td>Nontherapeutic</td>
<td>18 (45.5)</td>
</tr>
<tr>
<td>Preinjury clopidogrel</td>
<td>17 (7.6)</td>
</tr>
<tr>
<td>GCS score ≥13</td>
<td>33 (14.7)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>131 (58.2)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>26 (11.9)</td>
</tr>
<tr>
<td>Mortality after intracranial hemorrhage</td>
<td>21 (16.5)</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>8.1 (1–68)</td>
</tr>
</tbody>
</table>

GCS, Glasgow Coma Scale.

Table 2 Demographics by Presence (+) or Absence (−) of Intracranial Hemorrhage (ICH)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ICH(+) (n = 131)</th>
<th>ICH(−) (n = 94)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>79.4</td>
<td>79.6</td>
<td>0.84</td>
</tr>
<tr>
<td>Male</td>
<td>57 (43.9)</td>
<td>37 (39.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Fall</td>
<td>99 (75.6)</td>
<td>64 (68.1)</td>
<td></td>
</tr>
<tr>
<td>Pedestrian struck</td>
<td>24 (18.3)</td>
<td>20 (21.3)</td>
<td></td>
</tr>
<tr>
<td>Motor vehicle collision</td>
<td>0 (0.0)</td>
<td>6 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>8 (6.1)</td>
<td>4 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Preinjury aspirin</td>
<td>49 (37.7)</td>
<td>25 (26.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Preinjury clopidogrel</td>
<td>12 (9.2)</td>
<td>5 (5.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Warfarin group</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>17 (13.0)</td>
<td>5 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Nontherapeutic</td>
<td>9 (6.9)</td>
<td>9 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Nonuser</td>
<td>105 (80.2)</td>
<td>80 (85.1)</td>
<td></td>
</tr>
<tr>
<td>Mean presenting INR</td>
<td>1.53</td>
<td>1.28</td>
<td>0.06</td>
</tr>
<tr>
<td>Admission GCS score ≥13 points</td>
<td>23 (17.6)</td>
<td>10 (10.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mortality</td>
<td>21 (16.5)</td>
<td>5 (5.4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

INR, International Normalized Ratio; GCS, Glasgow Coma Scale.
Eighteen of 22 (81.8%) patients in the therapeutic group underwent immediate reversal of anticoagulation using both vitamin K and fresh frozen plasma (FFP) in each case. In one instance, recombinant factor VIIa was used in addition to vitamin K and FFP. Two of the four patients who did not undergo immediate reversal of anticoagulation presented with an ICH; reversal was not performed in these patients because of futility and concern for a thrombosis-related complication, respectively. The remaining two patients who did not undergo immediate reversal of anticoagulation did not present with an ICH. Compared with patients in the therapeutic group, patients in the nontherapeutic group were significantly less likely to undergo immediate reversal of anticoagulation (8 of 18 [44.4%], \( p = 0.002 \)). Seven of eight (87.5%) patients in the nontherapeutic group who underwent reversal of anticoagulation presented with an ICH, as compared with 2 of 10 (20.0%) of patients who did not undergo reversal. The INRs of the two patients who presented with an ICH but did not undergo immediate reversal of anticoagulation were 1.11 and 1.24, respectively. The lowest INR for which FFP was administered was 1.40.

A comparison of the therapeutic, nontherapeutic, and nonuser groups is shown in Table 3. There were no significant differences in age, gender, mechanism of injury, aspirin use, or clopidogrel use between groups. As expected, the mean INR was greatest in the therapeutic group (3.33; range, 2.13–7.28), followed by the nontherapeutic group (1.51; range, 1.00–1.96), and finally the nonuser group (1.11; range, 0.87–4.01). Eleven of the 22 patients in the therapeutic group had an admission INR ≥3 (50.0%). With the exception of ICH \( (p = 0.10) \), significant differences existed between groups with respect to the outcomes analyzed.

These relationships were explored further by calculating univariate odds ratios (ORs) for each outcome using the nonuser group as the reference category (Table 4, Fig. 1). As compared with the nonuser group, the therapeutic group was significantly more likely to present with a GCS score ≤13 (OR = 5.13, 95% confidence interval [CI] 1.97–13.39, \( p = 0.001 \)). Both overall mortality (OR = 4.48, 95% CI 1.60–12.50, \( p = 0.004 \)) and mortality after traumatic ICH (OR = 3.42, 95% CI 1.09–10.76, \( p = 0.03 \)) were also increased in the therapeutic group as compared with the nonuser group. However, no such relationships were observed when comparing the nontherapeutic group with the nonuser group. Furthermore, we observed a trend toward an increased likelihood of ICH in the therapeutic group as compared with the nonuser group (OR = 2.59, 95% CI 0.92–7.32, \( p = 0.07 \)). There was no difference in likelihood of ICH between the nontherapeutic and nonuser groups. Finally, a subgroup analysis of the therapeutic group revealed no difference in likelihood of ICH between those patients with an INR 2 to 3 (9 of 11, 81.8%) and an INR >3 (8 of 11, 72.7%) \( (p = 0.85) \).

### Table 3 Demographics by Warfarin Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Therapeutic (n = 22)</th>
<th>Nontherapeutic (n = 18)</th>
<th>Nonusers (n = 185)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>81.9</td>
<td>79.1</td>
<td>79.2</td>
<td>0.37</td>
</tr>
<tr>
<td>Male</td>
<td>10 (45.5)</td>
<td>7 (38.9)</td>
<td>77 (41.8)</td>
<td>0.91</td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>18 (81.8)</td>
<td>14 (77.8)</td>
<td>131 (70.8)</td>
<td>0.69</td>
</tr>
<tr>
<td>Pedestrian struck</td>
<td>3 (13.6)</td>
<td>3 (16.7)</td>
<td>38 (20.5)</td>
<td></td>
</tr>
<tr>
<td>Motor vehicle collision</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>1 (4.5)</td>
<td>1 (5.6)</td>
<td>10 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Preinjury aspirin</td>
<td>4 (19.0)</td>
<td>4 (22.2)</td>
<td>66 (35.7)</td>
<td>0.18</td>
</tr>
<tr>
<td>Preinjury clopidogrel</td>
<td>1 (4.6)</td>
<td>1 (5.6)</td>
<td>15 (8.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>Mean presenting INR*</td>
<td>3.33</td>
<td>1.51</td>
<td>1.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Admission GCS score ≤13 points</td>
<td>9 (40.9)</td>
<td>2 (11.1)</td>
<td>22 (11.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>17 (77.2)</td>
<td>9 (50.0)</td>
<td>105 (56.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>7 (31.8)</td>
<td>2 (11.8)</td>
<td>17 (9.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Mortality after ICH</td>
<td>6 (25.3)</td>
<td>1 (12.5)</td>
<td>14 (7.37)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* The mean presenting INR for each group was significantly different from that of each of the other two groups. INR, International Normalized Ratio; GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage.

### Table 4 Outcomes After Head Injury

<table>
<thead>
<tr>
<th>Group</th>
<th>OR</th>
<th>95% CI</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission GCS score ≤13 points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic group</td>
<td>5.13</td>
<td>1.97–13.39</td>
<td>0.001</td>
</tr>
<tr>
<td>Nontherapeutic group</td>
<td>0.93</td>
<td>0.20–4.30</td>
<td>0.92</td>
</tr>
<tr>
<td>Nonusers (reference category)</td>
<td>1.00</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic group</td>
<td>2.59</td>
<td>0.92–7.32</td>
<td>0.07</td>
</tr>
<tr>
<td>Nontherapeutic group</td>
<td>0.76</td>
<td>0.29–2.01</td>
<td>0.58</td>
</tr>
<tr>
<td>Nonusers</td>
<td>1.00</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Overall mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic group</td>
<td>4.48</td>
<td>1.60–12.50</td>
<td>0.004</td>
</tr>
<tr>
<td>Nontherapeutic group</td>
<td>1.28</td>
<td>0.27–6.07</td>
<td>0.76</td>
</tr>
<tr>
<td>Nonusers</td>
<td>1.00</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Mortality after ICH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic group</td>
<td>3.42</td>
<td>1.09–10.76</td>
<td>0.03</td>
</tr>
<tr>
<td>Nontherapeutic group</td>
<td>0.90</td>
<td>0.10–7.86</td>
<td>0.92</td>
</tr>
<tr>
<td>Nonusers</td>
<td>1.00</td>
<td></td>
<td>—</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage.
DISCUSSION

This study differentiates therapeutic from nontherapeutic elderly warfarin users in relation to risk of traumatic ICH and subsequent mortality. We found that, compared with nonusers, the therapeutic group incurred more severe traumatic brain injuries as evidenced by a significantly lower GCS score, a trend toward an increased likelihood of ICH, and a significantly increased likelihood of both overall mortality and mortality after ICH. However, none of these relationships were observed when comparing nontherapeutic warfarin users with nonusers.

These results have several implications in regard to the literature addressing preinjury warfarin use and traumatic brain injury. Most importantly, stratification of warfarin users by admission INR avoided potential masking of the relationship between anticoagulation and ICH because of nontherapeutic warfarin users. Incomplete INR information has obscured previous conclusions regarding this issue. For example, although Wojcik et al. reported no difference in intensive care unit length of stay, hospital length of stay, and overall mortality between warfarin users and nonusers among a statewide population of trauma patients with head injury, INR information was not available, precluding subgroup analysis. Matching based on severity of injury also precluded an analysis of the effects of warfarin therapy on this parameter. Such a collective analysis of warfarin users may have contributed to the failure to demonstrate an increased risk of ICH among warfarin users in similar, single-institution studies. Our observation that nearly one-half of warfarin users presented with an INR <2 suggests that collective grouping of warfarin users may be particularly misleading.

A second advantage of subgroup analysis of warfarin users by degree of anticoagulation involves elimination of potentially confounding differences between warfarin users and nonusers. Specifically, because, as compared with nonusers, warfarin users who sustain traumatic brain injury are, on average, older, present with more comorbidities, and are more likely to sustain injury as the result of a fall, one may postulate that overall health status, as opposed to warfarin use per se, is responsible for the observed adverse outcomes. However, failure to detect a difference in admission GCS score, likelihood of ICH, and mortality between nontherapeutic warfarin users and nonusers weakens this argument.

Despite the absence of a subgroup analysis of therapeutic as compared with nontherapeutic warfarin users, several recent studies have documented a relationship between preinjury warfarin use and both severity of traumatic brain injury and mortality. Lavoie et al. studied elderly (age ≥55 years) trauma patients who sustained closed head injuries from 1993 to 2001 at a single institution. After controlling for both comorbidities and mechanism of injury, warfarin users were more likely to have an Abbreviated Injury Score ≥4 for head injuries (OR = 2.43, 95% CI 1.10–5.17) and more likely to
die (OR = 2.73, 95% CI 1.22–6.12) as compared with nonusers. Karni et al. reviewed 278 elderly trauma patients from 1998 to 2000 with CT-documented ICH from a single institution. Compared with nonusers, warfarin users presented with a significantly lower GCS score (11.0 vs. 13.2) and incurred a higher 30-day mortality (50% vs. 20%). In a subgroup of patients with an INR >3.5, mortality approached 75%. Most recently, Franko et al. demonstrated a direct, linear relationship between degree of anticoagulation (grouped according to admission INR) and likelihood of both ICH and mortality among trauma patients. However, although it is suggested that nontherapeutic users and nonusers had similar results, they were not compared directly. These data, in addition to those present herein, support the hypothesis that therapeutic anticoagulation increases the likelihood of ICH and mortality after traumatic brain injury.

Although therapeutic as opposed to nontherapeutic anticoagulation was associated with adverse outcomes in the present study, it is unclear whether immediate reversal of anticoagulation may be withheld safely in nontherapeutic warfarin users who present with a traumatic ICH. In some cases, INR information may not become available until after the diagnosis of ICH is made, and the clinician must weigh the risks and benefits of immediate FFP transfusion. However, even when the INR is known at the time of diagnosis (as was the case for each patient in the current study), a striking amount of variability exists among trauma surgeons as to the INR above which reversal of anticoagulation should be implemented, the rapidity with which the prothrombin time is normalized, or the target INR after reversal. The current study was unable to address these questions because the majority of nontherapeutic patients with an ICH (8 of 10) received both FFP and vitamin K. By contrast, one recent study documented the efficacy of rapid reversal of anticoagulation with FFP among warfarin users with a therapeutic level of INR who had sustained a traumatic ICH. Future research is warranted to evaluate whether this benefit extends to nontherapeutic warfarin users and, if so, at what level of INR.

Our study is limited by a relatively small sample size, and thus, the inability to fully compare warfarin users with an INR of 2 to 3 to those with an INR >3. However, the proportions of patients in each group who sustained a traumatic ICH were comparable (9 of 11 [81.8%] vs. 8 of 11 [72.7%], respectively, p = 0.85). Furthermore, Ivascu et al. did not observe a difference in median INR when comparing therapeutic warfarin users with and without a traumatic ICH (2.7 vs. 2.5, respectively, p = 0.35). These observations suggest a threshold rather than a linear relationship between level of anticoagulation and risk of ICH, which is consistent with the exponential scale of the INR. However, both a small number of therapeutic users and a relatively narrow range of INRs among them (maximum INR = 7.28) precluded a more detailed test of this hypothesis. Adequately powered studies are needed to further analyze subgroups of therapeutic warfarin users.

We were also unable to explore the relationship between injury kinetics, warfarin use, and ICH because of lack of detailed kinetic data, as well as a high prevalence of low-velocity mechanisms. With regard to the observed differences between the therapeutic and nontherapeutic groups, the possibility remains that unmeasured factors may have predisposed the former to adverse outcomes, although there is no evidence to support this possibility. Finally, our sample was restricted to patients for whom the trauma service was consulted. However, because the index of suspicion for an ICH is heightened for warfarin users (and is especially high for therapeutically anticoagulated patients), we would expect this to result in an increased number of warfarin users with negative finding on CTH for whom a trauma consultation was obtained. This restriction would thus tend to underestimate the likelihood of ICH among warfarin users evaluated by the trauma service.

In conclusion, among elderly patients who had sustained a head injury, warfarin use with an admission INR ≥2 was associated with an increased severity of traumatic brain injury, a trend toward an increased likelihood of ICH, increased overall mortality, and increased mortality after ICH. Outcomes between nontherapeutic warfarin users and nonusers were comparable. These data suggest that therapeutic anticoagulation with warfarin, rather than unmeasured differences between warfarin users and nonusers, increases the likelihood of adverse outcomes after head trauma among elderly patients. By contrast, warfarin users who present with an INR ≤2 behave clinically in a fashion similar to nonusers. These data have implications for the management of warfarin users based on the degree of anticoagulation at admission, and support the growing literature describing the deleterious effects of therapeutic anticoagulation on outcomes after trauma in elderly patients. Larger studies are necessary to refine the evaluation of outcomes particularly with regard to level of anticoagulation.

ACKNOWLEDGMENTS

We thank Nayna Shah for her assistance with data compilation.

REFERENCES


The Scourge of Methamphetamine: Impact on a Level I Trauma Center

Sophia M. Swanson, BA, C. Beth Sise, JD, MSN, RN, Michael J. Sise, MD, Daniel I. Sack, BA, Troy Lisa Holbrook, PhD, MS, and Gabrielle M. Paci, BA

Background: Methamphetamine (METH) use is associated with high-risk behavior and serious injury. The aim of this study was to assess the impact of METH use in trauma patients on a Level I trauma center to guide prevention efforts.

Methods: A retrospective registry-based review of 4,932 consecutive trauma patients who underwent toxicology screening at our center during a 3-year period (2003–2005). This sample represented 76% of all trauma patients seen during this interval.

Results: From the first half of 2003 to the second half of 2005, overall use of METH increased 70% (p < 0.001), surpassing marijuana as the most common illicit drug used by the trauma population. Other illicit drug use did not significantly change during this interval.

METH-positive patients were more likely to have a violent mechanism of injury (47.3% vs. 26.3%, p < 0.001), with 33% more assaults (p < 0.01), 96% more gunshot wounds (p < 0.001), and 158% more stab wounds (p < 0.001). They were more likely to have attempted suicide (4.8% vs. 2.6%, p < 0.01), to have had an altercation with law enforcement (1.8% vs. 0.3%, p < 0.001), or been the victim of domestic violence (4.4% vs. 2.1%, p < 0.001). METH users had a higher mean Injury Severity Score (11.2 vs. 10.0, p < 0.01), were 62% more likely to receive mechanical ventilation (p < 0.001), and 53% more likely to undergo an operation (p < 0.001). They were more prone to leave against medical advice (4.9% vs. 2.1%, p < 0.001) and 113% more likely to die from their injuries (6.4% vs. 3.0%, p < 0.001). The average cost of care per METH user was 9% higher than that for nonusers, and METH users were more likely to be unfunded than nonusers (47.6% vs. 33.1%, p < 0.001). The annual uncompensated cost of care of METH users increased 70% during the study period to $1,477,108 in 2005.

Conclusion: METH use in trauma patients increased significantly and was associated with adverse outcomes and a significant financial burden on our trauma center. Evidence-based prevention efforts must be a priority for trauma centers to help stop the scourge of METH.

Key Words: Trauma centers, Methamphetamine, Drug abuse and injury, Screening and brief intervention, Injury prevention.

K
nown on the streets as “speed”, “meth”, “crank”, or in its pure form, “ice”, methamphetamine (METH) is a highly addictive synthetic stimulant that affects the central nervous system, producing feelings of prolonged euphoria, increased alertness, and decreased appetite. It is a white, odorless, bitter-tasting crystalline powder that dissolves readily in water or alcohol and comes in several forms that can be smoked, snorted, injected, or orally ingested. METH has a high potential for abuse because it is easy to use and cheap to manufacture from relatively inexpensive over-the-counter ingredients.

The volatile chemicals used to produce METH can create explosions, fires, and toxic fumes. Once dominated by motorcycle gangs and small local producers in the West, the METH market today includes organized Mexican sources smuggling large amounts of finished product to distributors throughout the United States.1,2

The now widespread availability of METH has led to an epidemic that threatens the entire country, with both urban and rural areas everywhere increasingly affected.3 According to a recent national survey, over 10 million Americans have tried METH at least once.4 Admissions for treatment of METH abuse have increased markedly in many states; for example, admissions for publicly funded treatment for METH in California alone increased 221% from 1993 to 2003.5 Drug-related emergency department (ED) visits involving stimulants, mostly METH, rose more than 50% nationally between 1995 and 2002.6 These increases are reflected in the National Institute for Justice’s Arrestee Drug Abuse Monitoring (ADAM) data. In 11 of the 39 ADAM sites studied in 2003, 25% or more of adult male arrestees tested positive for METH; only 1 ADAM site had a proportion that high in 1996.7,8

The increasing trends in METH use are of special concern because of the negative effects on individuals and related social costs. The associated behaviors of METH use, which include high-risk sexual activity,9 paranoia, violence, hallucinations, and sleeplessness,10 also place METH users at increased risk of violent and nonviolent injuries.11–13 As the

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From the Division of Trauma, Scripps Mercy Hospital, San Diego, California.
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Address for reprints: Michael J. Sise, MD, Division of Trauma, Scripps Mercy Hospital, 4077 5th Avenue, San Diego, CA 92103; email: sise.mike@scrippsh health.org.
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collectors of the results of high-risk behavior, trauma centers are well positioned to assess the impact of the use of this dangerous drug. Trauma centers also have a role in public health approaches aimed at preventing the problems caused by this malignant form of substance abuse.

We studied the impact of METH use by our trauma patients on mechanism, severity, and outcome of injury, and the use of hospital resources at a Level I trauma center in a large urban area in the Southwest United States. Our intent was to enlighten the trauma community about these aspects of METH use as a basis to guide prevention efforts.

PATIENTS AND METHODS

The Scripps Mercy Hospital Trauma Registry was retrospectively reviewed for patients admitted during the calendar years 2003, 2004, and 2005. The Scripps Mercy Hospital trauma catchment area lies within the urban center of San Diego County in Southern California. Data collection included alcohol and drug screening test results, demographic information, Injury Severity Score (ISS), mechanism of injury, hospital length of stay (LOS), patient outcomes, costs, charges, and reimbursement rates for care delivery. Admission to the intensive care unit (ICU) and the requirement for mechanical ventilation were considered dichotomous variables. Comparison was made between patients testing positive and negative for METH. Drug testing was performed with the TRIAGE urine assay.*

Our practice guideline during the study period was to obtain drug and alcohol screening for all trauma patients. Preformatted orders for alcohol and drug screening were written for all patients who came through the trauma room (TR). Blood alcohol was measured from blood samples taken in the TR, and toxicology screening from urine if the patient voided or had a Foley catheter inserted. If no urine was obtained in the TR, orders were sent with the patient to the inpatient unit for urine to be collected as soon as possible for a toxicology screening. Reasons for not obtaining a drug or alcohol test were examined. METH users commonly used other drugs and alcohol. As drug testing was frequently performed after in-hospital treatment, which included the administration of opiates and benzodiazepines, the testing results for these drugs were omitted from this analysis. The impact of additional drug and alcohol use was examined through multivariate analysis. When corrected for other drugs, alcohol, age, sex, and ISS, the associations between METH use and our outcome measures remained strong.

Statistical analysis was performed using Mantel-Haenszel $\chi^2$ (Epi Info v.3.3.2, Centers for Disease Control and Prevention, Atlanta, GA) for rates and proportions, and the Student’s $t$ test (Excel 2003, Microsoft, Redmond, WA) for quantitative variables. Multivariate analysis was conducted using SAS statistical analysis software (SAS version 6.12, SAS Institute, Cary, NC). The Scripps Mercy Hospital Institutional Review Board reviewed the design of the study, methods of data acquisition, and confidentiality protections, and approved the investigators to conduct the study.

RESULTS

There were 6,511 admissions during the study period, of which 4,932 (76%) patients were tested for drugs. The rate of METH-positive test results increased steadily during the study period (from 9.0% to 15.3%, $p < 0.001$). The frequency of positive test results for other illicit drugs, including marijuana (tetrahydrocannabinol [THC]), cocaine, barbiturates, and phencyclidine, did not change significantly and systematically during this time.

In the first half of 2003, METH was the second most common drug abused by the trauma population, after THC. By the second half of 2005, METH surpassed THC to become the most commonly used illicit drug (Fig. 1). Yearly testing rates were similar during the 3-year study period, with 1,584 (74.8%) patients tested the first year, 1,602 (76.0%) the second, and 1,746 (76.4%) the third.

Failure to perform a drug test was related to a variety of factors. Urinary catheter placement was reserved for unstable patients or those undergoing operation. If patients were uncooperative in using urine collection bottles or were discharged shortly after admission, testing was rarely possible. Patients whose initial workup was in the ED were tested less predictably. Drug screening frequency did not depend on age when only those patients who were initially admitted to our TR were considered. Drug screening was more common among men (73% vs. 64%, $p < 0.001$), African Americans (15% vs. 12%, $p < 0.01$), patients with a higher ISS (10.1 vs. 8.4, $p < 0.01$), those who were pedestrians hit by an automobile ($p < 0.05$), or those whose injuries resulted from an assault ($p < 0.01$).

Of the 4,932 patients tested for drugs from January 2003 to December 2005, 609 (12.3%) were found to be positive for METH. METH users were younger (32.7 years vs. 38.1 years, $p < 0.001$) and more likely to be men (80.6% vs. 72.0%, $p < 0.001$) and Hispanic (46.5% vs. 35.0%, $p < 0.001$). Assaults were 33% more likely (16.4% vs. 12.3%, $p < 0.01$), gunshot wounds almost twice as likely (11.0% vs. 5.6%, $p < 0.01$), and stab wounds more than twice as likely (19.9% vs. 7.7%, $p < 0.001$) among METH-positive patients (Table 1). The demographic make-up of the METH-positive population was similar for each year of the study.

When adjusted for other drugs, METH-positive patients had a higher mean ISS than METH-negative patients had (10.8 vs. 10.0, $p = 0.06$). When adjusted for other drugs, age, sex, and ISS, our outcome measures were unchanged (Table 2). METH-positive patients were twice as likely to be associated with high-risk behavior, trauma centers are well positioned to assess the impact of the use of this dangerous drug. Trauma centers also have a role in public health approaches aimed at preventing the problems caused by this malignant form of substance abuse.

We studied the impact of METH use by our trauma patients on mechanism, severity, and outcome of injury, and the use of hospital resources at a Level I trauma center in a large urban area in the Southwest United States. Our intent was to enlighten the trauma community about these aspects of METH use as a basis to guide prevention efforts.

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Statistical analysis was performed using Mantel-Haenszel $\chi^2$ (Epi Info v.3.3.2, Centers for Disease Control and Preven-
associated with a violent mechanism of injury \((p < 0.001)\). Self-inflicted injuries were 70% more likely \((p < 0.05)\) among METH users, and domestic violence was more than twice as common \((p < 0.001)\). Involvement of law enforcement was significantly higher in METH users, represented by a nearly five-fold increase over nonusers \((p < 0.001)\). Forty-four percent of the patients whose injury resulted from law enforcement intervention were positive for METH. METH users tended to have a longer hospital LOS (although this was not found to be significant) and 50% more likely to undergo one or more operations \((p < 0.001)\). METH users were more than twice as likely to leave against medical advice \((p < 0.001)\) and to die from their injuries \((p < 0.001)\). The addition of alcohol to the models did not materially affect the results.

METH-positive patients were likely to be polydrug users, with 41% of METH users also testing positive for marijuana, cocaine, and other drugs. Demographic, injury, and outcome trends remained the same after adjusting for these drugs. Polydrug users who were METH-positive were more likely to be uninsured compared with polydrug users who were METH-negative \((p < 0.001)\). There was

| Table 1 Demographics, Mechanism of Injury, and Clinical Course in METH-Positive and METH-Negative Patients |
|-------------------------------------------------|---------------------------------|-------------|
| Demographics                                   | METH (+) \(n = 609\) | METH (-) \(n = 4,323\) | \(p\) |
| Age (mean)                                     | 32.7                | 38.1           | <0.001  |
| Sex (male)                                     | 491 (81)*           | 3,113 (72)     | <0.001* |
| ISS (mean)                                     | 11.2*               | 10.0           | <0.01*  |
| Ethnicity                                      |                     |                |         |
| White                                          | 216 (35)            | 1,749 (40)     | <0.05   |
| African American                               | 75 (12)             | 682 (16)       | <0.05   |
| Hispanic                                       | 283 (46)*           | 1,515 (35)     | <0.001* |
| Asian                                          | 15 (2)              | 188 (4)        | <0.05   |
| Other                                          | 20 (3)              | 189 (4)        | NS      |
| Insurance                                      |                     |                |         |
| Uncompensated/indigent                         | 290 (48)*           | 997 (23)       | <0.001* |
| Other                                          | 256 (41)*           | 91 (2)         | <0.001* |
| Mechanism of injury                            |                     |                |         |
| MVC                                            | 166 (27)            | 1,755 (41)     | <0.001  |
| PvA                                            | 56 (9)              | 322 (7)        | NS      |
| Fall                                           | 60 (10)             | 930 (22)       | <0.001  |
| Assault                                        | 100 (16)*           | 533 (12)       | <0.01*  |
| GSW                                            | 67 (11)*            | 242 (6)        | <0.001* |
| Stab wound                                     | 121 (20)*           | 335 (8)        | <0.001* |
| Other                                          | 39 (6)              | 206 (5)        | NS      |
| Clinical course                                |                     |                |         |
| Hospital LOS (d)                               | 4.3                 | 3.7            | NS      |
| ICU LOS (d)                                    | 1.2                 | 1.1            | NS      |
| Cost of care (mean)                            | $15,295*            | $14,040        | <0.05*  |

Values inside parentheses indicate percentage values.

* Significant positive associations with METH.

METH (+), tested positive for methamphetamine; METH (-), tested negative for methamphetamine; ISS, Injury Severity Scale; MVC, motor vehicle crash; PvA, pedestrian struck by an automobile; GSW, gunshot wound; LOS, length of stay; ICU, intensive care unit; $, US$; NS, not significant.
no recidivism among METH-positive patients during the 3-year study interval.

Of all other drug and alcohol users, METH users were most likely to be uninsured. Overall, 48% of METH-positive patients had no health insurance compared with 22% of drug-free patients. METH users were significantly less likely to be insured by Medicare, MediCal, private insurance, third party insurance, and military insurance \((p < 0.001)\). They were also less likely to be employed before injury \((40.5\% \text{ vs. } 49.4\%, p < 0.01)\).

The cost of care per METH-positive patient was 9\% higher than per METH-negative patients, with an average cost of $15,295 versus $14,040, \(p < 0.05\). Although METH-positive patients represented 13\% of the total cost to the hospital and 9\% of the potential revenue, they were 34\% less likely to pay their bills. METH-positive patients had a payment:charge ratio of 0.17, whereas METH-negative patients had a ratio of 0.33. The average uncompensated cost per METH patient was $9,770. The average uncompensated annual cost was $944,473, and the total uncompensated cost of caring for METH patients during the 3-year study period was $2,833,417 (Fig. 2).

**DISCUSSION**

METH is an extremely powerful stimulant with significant physical and behavioral effects. It is easy to produce, ubiquitous in its availability, and represents a major threat to the health and welfare of every community where it has become a popular drug of abuse. The pharmacokinetics, short- and long-term effects, and associated critical care issues are summarized in Table 3. This drug becomes a major factor at the trauma centers in each community it affects.

Our Level I trauma center experienced a marked increase in METH use by our patients during this recent 3-year study interval. Overall, METH users were more commonly injured during violent or illegal activity, more severely injured, and more likely to die from their injuries than non-METH users. The majority of these patients were men and predominantly Hispanic and white. They were also less likely to have health insurance, and their care, therefore, represented an increasingly significant financial burden for our trauma center.

During the 3-year study, METH use among our trauma patients increased by 70\% (from 9.0\% to 15.3\%), whereas METH use in the general population in the State of California remained stable at a rate of approximately 5\%.\(^4\) We experienced an overall increase of 14.5\% in trauma patient volume during this period, which resulted in our seeing nearly twice as many METH users in late 2005 compared with early 2003. This increase was in contrast to relatively stable rates of patients with positive test results for alcohol and other drugs. We also observed a fairly high rate (41\%) of polydrug use in our METH-positive patients.

When we examined possible causes of the significant increase of METH use among our patients, we discovered a worrisome trend. According to national drug intelligence,\(^31\) recent success in reducing domestic METH production through chemical precursor sales restrictions and law enforcement efforts have resulted in a significant shift in the

<table>
<thead>
<tr>
<th>Variable</th>
<th>METH (+) ((n = 609)) (%)</th>
<th>METH (-) ((n = 4,323)) (%)</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>Adjusted OR*</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Violence</td>
<td>47</td>
<td>26</td>
<td>2.5†</td>
<td>2.1–3.0</td>
<td>2.0†</td>
<td>(1.6–2.4)</td>
</tr>
<tr>
<td>Suicide</td>
<td>5</td>
<td>3</td>
<td>1.9†</td>
<td>1.2–2.9</td>
<td>1.7§</td>
<td>(1.1–2.6)</td>
</tr>
<tr>
<td>Law enforcement involved</td>
<td>2</td>
<td>0.3</td>
<td>5.7†</td>
<td>2.6–12.5</td>
<td>4.8†</td>
<td>(2.1–10.8)</td>
</tr>
<tr>
<td>Domestic violence</td>
<td>4</td>
<td>2</td>
<td>2.2†</td>
<td>1.4–3.3</td>
<td>2.5†</td>
<td>(1.6–3.9)</td>
</tr>
<tr>
<td>Surgery</td>
<td>29</td>
<td>19</td>
<td>1.7†</td>
<td>1.4–2.1</td>
<td>1.5†</td>
<td>(1.2–1.9)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>21</td>
<td>13</td>
<td>1.7†</td>
<td>1.4–2.2</td>
<td>1.6†</td>
<td>(1.3–2.1)</td>
</tr>
<tr>
<td>Mortality</td>
<td>6</td>
<td>3</td>
<td>2.2†</td>
<td>1.5–3.2</td>
<td>2.3†</td>
<td>(1.5–3.7)</td>
</tr>
<tr>
<td>Left against medical advice</td>
<td>5</td>
<td>2</td>
<td>2.4†</td>
<td>1.6–3.7</td>
<td>2.2†</td>
<td>(1.4–3.3)</td>
</tr>
</tbody>
</table>

* Adjusted OR was adjusted for other drugs, ISS, age, and sex. Results did not materially change when alcohol was added to the models.
† \(p < 0.001\).
‡ \(p < 0.01\).
§ \(p < 0.05\).
METH market. After a sharp decrease in METH production in the United States (METH laboratory seizures nationally decreased 42% from 2004 [10,015] to 2005 [5,846]), most production and distribution was consolidated under the control of Mexican drug trafficking organizations. These Mexican drug trafficking organizations typically produce ice, a highly pure form of METH that is smoked, potentially causing a more rapid onset of addiction to METH. The increasing availability of ice in our region, reflected in drug seizure data at the United States-Mexico border since 2003, may have contributed to the increased incidence of METH-positive trauma patients. It also may explain the more than 40% increase in METH-related ED visits in our metropolitan area between 1995 and 2002.6

These findings are echoed in a recent survey of hospital ED officials in 39 states about the effect of METH on county public hospitals.32 The results showed that there were more METH-related ED visits than any other drug. Forty-seven percent of the 200 responding hospitals reported METH as the top illicit drug involved in ED visits. Seventy-three percent reported that emergency room presentations involving METH increased during the last 5 years; 68% reported continuing increases during the last 3 years. Eighty-three percent said that patients presenting with a METH-related emergency are often uninsured and 56% reported costs have increased at their facilities because of the growing use of METH.

Our study findings also compare with other research studies on METH use in urban trauma centers. In a 5-year review of trauma patients admitted to a Level I trauma center in California, researchers reported an 81% increase in METH use with a minimal increase in the use of cocaine and a decrease in positive blood alcohol rates.11 Patients who were METH-positive were also most likely to be white or Hispanic. Likewise, in a 6-month retrospective study comparing 461 METH-positive patients and all others presenting to the ED at the same Level I trauma center, researchers reported that METH-positive patients were most commonly white men who lacked health insurance; polydrug use was also noted.33 The association of METH and polydrug use is further confirmed in studies of drug use trends among arrestees in five western cities,34 and national data on drug-related ED visits.6

The METH-positive patients in our study were significantly more likely to have a violent mechanism of injury with 33% more assaults, 96% more gunshot wounds, and 158% more stab wounds. They were also significantly more likely to have attempted suicide, had an altercation with law enforcement, or been the victim of domestic violence.

The literature exploring the nature of METH use generally shows a link with violence, describing METH users as both the perpetrators35 and the victims of interpersonal violence.36 It also reveals that METH users experience high levels of psychiatric symptoms, particularly depression and attempted suicide, but also anxiety and psychotic symptoms.37 Combined with the drug’s deleterious effects on psychomotor performance, known to contribute to non-violent mechanisms of injury such as motor vehicle crashes,33,38 METH’s association with violence raises the risk of injury to users and nonusers alike. The link between METH and violence was nonetheless not a consistent finding in other recent studies involving trauma patients. In one such study,11 METH use was most commonly associated with vehicular trauma, whereas cocaine use was associated with interpersonal violence. Moreover, METH users’ mechanism of injury profile was similar to that associated with alcohol. Although a study of emergency patients found a significant association between METH use and injury from trauma,33 the majority of injuries were caused by blunt trauma such as motor vehicle crashes. In contrast, a study of 212 minimally injured trauma patients in Hawaii revealed that METH-positive patients were more likely to have intentional self-inflicted injury or intentional assaults than were those who tested negative.13

### Table 3 Methamphetamine—Pharmacokinetics, Effects, and Critical Care Issues

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Mechanism of action</th>
<th>Increases release and blocks reuptake of central neurotransmitters (dopamine, norepinephrine, serotonin)16,17 leading to neurotoxicity and neurodegeneration16,19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Smoked, snorted, injected, or orally ingested20</td>
<td></td>
</tr>
<tr>
<td>Duration of “high”</td>
<td>4–12 h or more, depending on amount taken21</td>
<td></td>
</tr>
<tr>
<td>Plasma half life</td>
<td>9–15 h; excretion is enhanced by urinary acidification22</td>
<td></td>
</tr>
</tbody>
</table>

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**Pharmacokinetics**

**Mechanism of action** Increases release and blocks reuptake of central neurotransmitters (dopamine, norepinephrine, serotonin), leading to neurotoxicity and neurodegeneration.

**Route of administration** Smoked, snorted, injected, or orally ingested.

**Duration of “high”** 4–12 h or more, depending on amount taken.

**Plasma half life** 9–15 h; excretion is enhanced by urinary acidification.

**Short-term effects**

- Increased attention, increased activity, decreased fatigue, euphoria, anorexia, high-risk sexual activity, tachypnea, tachycardia/arrhythmia, hypertension, hyperthermia.

**Long-term effects**

- Addiction, psychosis (paranoia, hallucinations, repetitive activity), neurotransmitter depletion.

**Critical care issues**

- Prolonged/high-intensity use can cause a variety of complications, the most relevant being metabolic acidosis resulting from peripheral vasoconstriction and regional ischemia; rhabdomyolysis secondary to muscle ischemia induced by arterial vasoconstriction; ischemic stroke secondary to cerebral vasoconstriction; myocardial infarction and arrhythmia secondary to regional cardiac ischemia; hypotension due to loss of autonomic regulation from norepinephrine depletion; and disseminated intravascular coagulation due to massive clotting triggered by hyperpyrexia.

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The reason for the inconsistent association of METH and violence in these studies is unclear. Some suggest that a drug testing bias may influence the rate of a violent injury mechanism in the subject trauma populations. In our study, we attempted to limit the possibility of testing bias by accomplishing a high rate of testing. We, in fact, tested for drugs at a significantly higher rate (75.7%) compared with rates achieved in other published studies of METH use in trauma and ED patients (e.g., Richards et al., 12.8%; Tominaga et al., 57.2%; p < 0.001).

The METH users in our study had a higher ISS, were 62% more likely to receive mechanical ventilation, and 53% more likely to undergo an operation. They were more prone to leave against medical advice and more than twice as likely to die from their injuries. This propensity for more significant injuries and poor outcomes among METH users coupled with a higher rate of not having health insurance resulted in a predictably negative impact on the trauma center’s finances.

The correlation of METH use and these financial outcomes was not consistently found in other major studies of injured METH users. We examined actual charge, cost, and revenue data to assess hospital resource use. In contrast, these other studies used surrogate indicators, including rates of emergency surgery and ICU admission, or hospital LOS and charges. These surrogates for hospital resource use may be less accurate indicators of financial impact compared with actual cost and revenue data. In addition, our much higher rate of drug testing compared with that used in the other studies may well have resulted in a stronger correlation of METH use with these outcomes.

The future burden, financial and medical, of METH-positive trauma patients may be reduced through evidence-based substance abuse prevention strategies. It is vital for trauma centers to institute protocols that effectively identify and assist these patients, similar to screening and brief intervention for at-risk and dependent drinkers. Trauma centers should also become involved in community efforts to reduce METH use and the associated negative health and social consequences.

CONCLUSION

METH use increased significantly in our patients and was associated with a variety of adverse outcomes and a significant financial burden on our trauma center. A better understanding of the medical and financial impact of METH is imperative to the development and implementation of effective prevention strategies. Evidence-based substance abuse prevention efforts must be a priority for trauma centers to help stop the scourge of METH.

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Penetrating injuries to the torso can present a diagnostic and therapeutic dilemma. Patients with hemodynamic instability should be treated with rapid operative exploration. Patients who present with normal vital signs without obvious indication for surgical intervention can be managed using a variety of algorithms. Some have advocated expectant management with serial physical examination, whereas others have been proponents of mandatory exploration with either laparotomy or laparoscopy depending on location and type of penetrating injury. Computed tomography (CT) scanning is also frequently used to evaluate patients with penetrating torso trauma.

A primary consideration in the patient who does not undergo operative evaluation after penetrating torso trauma is the concern for missed injuries. The diaphragm is an organ that has been notoriously difficult to evaluate without operative intervention, and missing diaphragm injuries may have significant implications for long-term morbidity and mortality. Studies examining the use of conventional CT scan to detect and exclude diaphragm injuries after blunt trauma have reported sensitivities as low as 14% to 73% and specificities of 76% to 99%. Using spiral CT with coronal and sagittal reconstructions, the reported sensitivities to detect blunt diaphragm injury in one series was still only 50% for injuries on the right side and 78% for injuries on the left. In another small retrospective study that included patients who sustained blunt and penetrating injuries, sensitivity and specificity were reported to be only 84% and 77%, respectively. With the increasing availability of multidetector row CT (MDCT) in most trauma centers, the high-resolution axial, coronal, and sagittal reformatted images may help to significantly improve the detection accuracy of diaphragm injury over what has been previously reported. We hypothesize that MDCT is an accurate diagnostic imaging technique for detection of diaphragm injuries in patients who have sustained penetrating trauma to the torso.

Background: The use of computed tomography (CT) to identify injury after penetrating torso trauma has become routine in the hemodynamically stable patient. The diaphragm has been a historically difficult structure to evaluate, however, and missed injuries to the diaphragm may result in significant morbidity. With the increasing use of multidetector row CT (MDCT), we hypothesized that CT would be an accurate detection modality to identify patients with diaphragm injuries.

Methods: We retrospectively reviewed the admission CT of consecutive patients admitted for penetrating injury to the torso during a 4-year period. The CT scans were reviewed and classified into three categories: positive (P), negative (N), or equivocal (Eq). Data from the medical records of these patients were abstracted to identify demographics, injury-specific data, length of stay, length of follow-up (LOFU), and operative findings.

Results: There were 803 patients who met inclusion criteria. Mechanism of injury was gunshot wound in 36% and stab wound in 64%. Mean length of stay was 4 days (±6.6) and mean length of follow-up was 43 days (±184). CT was read as P in 57, N in 710, and Eq in 36 patients. Diaphragm injury was detected in 67 patients overall and was excluded in 736. For the entire study population, sensitivity and specificity were calculated as 94.0% (95% CI = 88.4–99.7) and 95.9% (94.5–97.4) with an overall accuracy of 95.8% (94.4–97.2) if the CT scan was used to exclude diaphragm injury ([P and Eq] vs. N). Sensitivity and specificity were 82.1% (72.9–91.3) and 99.7% (99.4–100) if CT was used to detect diaphragm injury (P vs. [N and Eq]). One hundred and forty-eight patients underwent operative procedures in which the diaphragm was evaluated. Diaphragm injury was identified in 50 (38 P, 4 N, 8 Eq) and was surgically excluded in 104 patients (2 P, 93 N, 9 Eq). Three hundred and eighty-four patients were lost to follow-up; including 348 who had negative finding on CT. There were no known missed diaphragm injuries during the study period or in follow-up.

Conclusions: Injuries to the diaphragm occur commonly after penetrating torso trauma. MDCT scan is an accurate test to detect diaphragm injury. When MDCT is equivocal, further investigation is required to evaluate the diaphragm.

Key Words: Torso trauma, Diaphragm injury, CT scan, Diagnosis.

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From the Program in Trauma, R Adams Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, Maryland.
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Address for reprints: Deborah M. Stein, MD, MPH, Division of Critical Care/Program in Trauma, R Adams Cowley Shock Trauma Center, University of Maryland Medical Center, 22 South Greene Street, Baltimore, MD 21201; email: dstein@umm.edu.
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Penetrating Injuries to the Torso: A Diagnostic and Therapeutic Dilemma

Deborah M. Stein, MD, MPH, Gregory B. York, MD, Sharon Boswell, ACNP, Kathirkamanthan Shanmuganathan, MD, James M. Haan, MD, and Thomas M. Scalea, MD

Accuracy of Computed Tomography (CT) Scan in the Detection of Penetrating Diaphragm Injury

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PATIENTS AND METHODS

This study was conducted at the R Adams Cowley Shock Trauma Center of the University of Maryland School of Medicine. The Shock Trauma Center trauma registry was used to identify all patients admitted between January 2000 and December 2004 who sustained penetrating torso trauma and underwent intravenous contrast-enhanced MDCT scan of the chest, abdomen, or both as part of their initial diagnostic evaluation at the discretion of the attending surgeon. Patients who sustained penetrating injuries to the groin, buttock, upper back, or upper chest were excluded. The admission scans were performed on a 4- or 16-slice MDCT scanner (MX 8000 or Brilliance 16 Power; Philips Medical Systems, Cleveland, OH) using a detector width of 1 mm or 0.75 mm and pitch of 1 or 0.98, respectively. Triple contrast material was administered and included oral, rectal and 150 mL of I2 mg/mL of intravenous contrast material. Soft-copy axial images, 3 mm or 5 mm thickness, were reviewed by board-certified radiologists. Soft-copy reformatted sagittal and coronal images were also reviewed when available. The radiologists reviewed the CT scans at the time of patient presentation, as part of our institution’s routine radiographic standard of care.

The CT scan reports of the patients were reviewed and classified into three categories; positive (P; injury was detected), negative (N; no injury was detected), and equivocal (Eq; results were inconclusive). MDCT findings that were considered positive resulting in a diagnosis of diaphragm injury included (1) discrete disruption of the diaphragm, (2) herniation of abdominal viscera into the thoracic cavity, (3) contiguous injuries on either side of the diaphragm, especially in patients with stab wounds or only one trajectory of penetration, (4) foreign body within the muscle of the diaphragm itself, and (5) diaphragmatic defects with fat herniation.

Findings that were considered equivocal included (1) pleural effusions, lung contusion, or hemothoraces that obscured the outline of the diaphragm, (2) thickening of the diaphragm as a result of edema, hematoma, or blood tracking along the diaphragm, (3) ballistic fragments that caused artifact in the region of the diaphragm, (4) a wound tract outlined by air, blood from wounding, bullet or bone fragments extending up to the diaphragm, and (5) proximity of the tract of penetration near the diaphragm without discrete injury.

Negative CTs included (1) those in which the tract of penetration was remote from the diaphragm, (2) the tract was extracavitary, and (3) if the diaphragm was fully visualized without any of the aforementioned findings.

The medical records of all patients were then reviewed for operative findings, injury-specific data, demographics, hospital length of stay, and duration of follow-up of patients. Diagnostic effectiveness statistics were calculated using simple interactive statistical analysis. The Institutional Review Board of the University of Maryland School of Medicine approved this study.

RESULTS

There were 803 patients who met inclusion criteria for this study. Table 1 depicts the demographic information of the study population. Nearly 90% of the patients were male and in 64% the mechanism of injury was a stab wound. Mean length of stay for the entire cohort was 4 (±6.6) days. Mortality in these patients was 1.1%.

The MDCT scan reports of the 803 patients were reviewed. Fifty-seven CT scans showed positive findings for diaphragm injury (Fig. 1), 710 showed negative findings for diaphragm injury, and in 36 CT scans, a diaphragm injury could not be excluded and were reported as equivocal (Fig. 2). By comparing the radiology and operative reports of 57 patients with a CT scan showing positive findings for diaphragm injury it was found that there were 55 true-positive CTs and 2 false-positive CTs. We reviewed the medical records and operative and radiology reports of 710 patients with CTs showing negative findings for diaphragm injury. Of

Table 1 Demographics of Study Population (N = 803)

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td>(n = 803)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>99</td>
<td>(12.3)</td>
</tr>
<tr>
<td>Male</td>
<td>704</td>
<td>(87.7)</td>
</tr>
<tr>
<td>Mechanism of injury, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stab wound</td>
<td>512</td>
<td>(63.8)</td>
</tr>
<tr>
<td>GSW</td>
<td>291</td>
<td>(36.2)</td>
</tr>
<tr>
<td>Discharge disposition, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Nonmedical*</td>
<td>696</td>
<td>(86.7)</td>
</tr>
<tr>
<td>Expired</td>
<td>9</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Acute care</td>
<td>21</td>
<td>(2.6)</td>
</tr>
<tr>
<td>Rehabilitation center</td>
<td>53</td>
<td>(6.6)</td>
</tr>
<tr>
<td>Psychiatric facility</td>
<td>19</td>
<td>(2.4)</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>(0.6)</td>
</tr>
<tr>
<td>Thorax AIS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>249</td>
<td>(31.0)</td>
</tr>
<tr>
<td>1</td>
<td>177</td>
<td>(22.0)</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>(1.5)</td>
</tr>
<tr>
<td>3</td>
<td>302</td>
<td>(37.6)</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>(7.5)</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>(0.4)</td>
</tr>
<tr>
<td>Abdomen AIS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>336</td>
<td>(41.8)</td>
</tr>
<tr>
<td>1</td>
<td>292</td>
<td>(36.4)</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>(10.7)</td>
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<tr>
<td>3</td>
<td>67</td>
<td>(3.8)</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>(2.2)</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Age (yr), mean (SD)</td>
<td>29.6</td>
<td>(11.4)</td>
</tr>
<tr>
<td>ISS, mean (SD)</td>
<td>9.9</td>
<td>(9.7)</td>
</tr>
<tr>
<td>Admission RTS, mean (SD)</td>
<td>7.69</td>
<td>(0.65)</td>
</tr>
<tr>
<td>TRISS, mean (SD)</td>
<td>0.969</td>
<td>(0.098)</td>
</tr>
<tr>
<td>LOS (days), mean (SD)</td>
<td>4</td>
<td>(6.8)</td>
</tr>
<tr>
<td>Length of follow-up (days after discharge), mean (SD)</td>
<td>43</td>
<td>(184)</td>
</tr>
</tbody>
</table>

* Includes patients discharged to home, shelter, or police custody.

GSW, Gunshot wound; AIS, Abbreviated Injury Scale; ISS, Injury Severity Score; RTS, Revised Trauma Score; TRISS, Trauma Score-Injury Severity Score; LOS, Length of Stay.
those reviewed, 706 were true-negative CTs and 4 CTs were false-negatives. All four patients with false-negative CTs had proximity injuries evidenced by a wound tract near the diaphragm as demonstrated by CT. The 36 patients with equivocal CT reports for diaphragm injury included 8 patients who were then found to have a diaphragm injury at surgery. Surgery (n = 9) or clinical follow-up (n = 19) indicated that the diaphragm was intact in the remaining 28 patients in the equivocal CT group. Table 2 depicts the results of MDCT in all study patients.

One hundred and fifty-four of the patients in this study population underwent operative procedures during which the diaphragm was evaluated. A diaphragm injury was seen at surgery in 50 patients and the diaphragm was intact in 104 patients. Among the surgical group, the MDCT reports were true-positive in 48 patients, true-negative in 97 patients, and equivocal in 17. There were two false-positive and four false-negative results in the surgically validated group. Table 3 depicts the results of MDCT in all patients with the diagnosis of diaphragm injury surgically validated. Primary surgical evaluation was accomplished with laparotomy in 123, laparoscopy in 6, thoracotomy in 21, and thoracoscopy in 4.

Mean length of follow-up for the entire study group of 803 patients was 43 (±104) days. Three hundred and eighty-four patients were completely lost to follow-up (47.8%), including 348 patients who underwent an MDCT, which showed negative findings. Clinical follow-up with a history and physical examination was available in 360 of the patients with negative findings on CT scans. Of the 613 patients with negative findings on CT scans who did not have surgical confirmation, a follow-up clinic visit was attended at 1 week.
or later by 239 patients. Twenty-one patients were followed up for greater than 6 months. There were no known missed diaphragm injuries in this group.

When MDCT was used as a diagnostic test to evaluate the diaphragm in patients with penetrating trauma to the torso (P vs. [N and Eq]), the sensitivity and specificity were 82% and 100%, respectively. The accuracy was 96%. MDCT was able to exclude a diaphragm injury ([P and Eq] vs. N) in this group of patients with a sensitivity of 94%, specificity of 96%, and an overall accuracy of 96%. In patients in whom the diaphragm was surgically evaluated, the sensitivity, specificity, and accuracy for MDCT to detect diaphragm injury (P vs. [N and Eq]) was 76%, 98%, and 91%, respectively. The sensitivity and specificity for MDCT to exclude diaphragm injury ([P and Eq] vs. N) in patients in whom the diaphragm injury was surgically validated were 92% and 89%, respectively, with an overall accuracy rate of 90%. Kappa agreement was excellent for the use of MDCT to either detect or exclude diaphragm injury after penetrating trauma (Table 4).

Table 3 Results of MDCT in Patients in Whom Diaphragm Injury Was Surgically Evaluated

<table>
<thead>
<tr>
<th></th>
<th>Diaphragm Injury</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CT was used to exclude diaphragm injury</td>
<td>P and Eq</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>50</td>
</tr>
<tr>
<td>CT was used to detect diaphragm injury</td>
<td>P</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>N and Eq</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 4 Diagnostic Effectiveness of MDCT

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>Kappa Measure of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results in all patients if CT was used to exclude diaphragm injury</td>
<td>94.0 (88.4–99.7)</td>
<td>95.9 (94.5–97.4)</td>
<td>67.7 (58.2–77.2)</td>
<td>99.4 (97.9–100)</td>
<td>95.8 (94.4–97.2)</td>
<td>0.765 (0.697–0.833)</td>
</tr>
<tr>
<td>Results in all patients if CT was used to detect diaphragm injury</td>
<td>82.1 (72.9–91.3)</td>
<td>99.7 (99.4–100)</td>
<td>96.5 (91.7–100)</td>
<td>98.4 (95.1–100)</td>
<td>98.2 (97.4–99.2)</td>
<td>0.878 (0.809–0.947)</td>
</tr>
<tr>
<td>Results in patients in whom diaphragm injury was surgically validated if CT was used to exclude diaphragm injury</td>
<td>92.0 (84.5–99.5)</td>
<td>89.4 (83.5–95.3)</td>
<td>80.7 (70.5–90.9)</td>
<td>95.9 (90.7–100)</td>
<td>90.2 (85.6–94.9)</td>
<td>0.786 (0.629–0.943)</td>
</tr>
<tr>
<td>Results in patients in whom diaphragm injury was surgically validated if CT was used to detect diaphragm injury</td>
<td>76.0 (64.2–100)</td>
<td>98.1 (95.4–100)</td>
<td>95.0 (88.2–100)</td>
<td>89.5 (80.0–99.0)</td>
<td>90.9 (86.4–95.4)</td>
<td>0.781 (0.625–0.937)</td>
</tr>
</tbody>
</table>

Values given are percent (95% confidence interval) values.

DISCUSSION

Injuries to the diaphragm are common after penetrating trauma. Diaphragm injuries may occur twice as commonly after penetrating trauma as in patients who sustain blunt mechanisms of injury. Some studies suggest that diaphragmatic injuries occur in up to 7% of patients with penetrating trauma to the torso, whereas other studies detected a rate of 20% to 40% with penetrating thoracoabdominal injuries. Associated injuries to chest and abdominal viscera are common and are largely dependent on the type and trajectory of the missile or projectile.

Diagnosis of these injuries can present a significant challenge, however. The only gold standard for diagnosis of diaphragmatic injuries is operative evaluation; therefore, the need for noninvasive accurate tests to diagnose and exclude these injuries is needed. In the hemodynamically stable patient presenting with penetrating injury to the torso, CT has been demonstrated to be an accurate and efficacious test to evaluate for peritoneal violation and predict the need for laparotomy. Penetrating diaphragm injuries are notoriously difficult to visualize with spiral CT scan secondary to their typically small size and lack of visceral herniation. The use of reformatted sagittal and coronal images may be helpful in visualizing these injuries. Reported sensitivity and specificity of CT to detect diaphragm injuries range widely in the literature from sensitivities of 14% to 78% and specificities of 76% to 100%. Some advocate the use of magnetic resonance imaging for diaphragmatic injuries, but this technique has not gained widespread use in the acute setting. Laparoscopy has been used with increasing frequency in patients with penetrating injuries without other indications for exploration to exclude peritoneal violation and to evaluate the diaphragm. One small prospective study reported a sensitivity and specificity...
of laparoscopy to detect diaphragm injury of 87.5% and 100%, respectively. Others advocate a combined use of CT scan and laparoscopy after penetrating flank trauma to fully evaluate the diaphragm and prevent missed injuries. Alternatively, video-assisted thoracoscopic has been used by some to surgically evaluate for the presence of a diaphragm injury.

In a study published in 2001, CT failed to detect a single diaphragmatic injury in 11 patients who sustained penetrating thoracoabdominal trauma. In a prospective trial from our institution using spiral CT scan, CT failed to identify one diaphragm injury for a failure rate of 17%. However, this study was conducted before the use of the 16-slice MDCT at our institution. The authors of this study concluded that, in patients with suspected diaphragm injury after penetrating trauma, additional investigation was warranted. In another trial from our institution that included patients from both the single-detector and four-slice MDCT era, specific CT findings of diaphragm injury were found in only 40% of patients, whereas diaphragm injury could not be excluded in 88% of patients secondary to the extension of the wound tract to the diaphragm.

In this retrospective study, we demonstrate that MDCT is a highly accurate test to identify diaphragmatic injuries after penetrating trauma to the torso. This could be attributed to the high-resolution axial and reformatted images that are obtained with 4- and 16-slice MDCT. When used as a diagnostic test, specificity approaching 100% was achieved. Similarly, if used to clearly exclude diaphragm injuries, MDCT had a sensitivity of 94%. The use of MDCT in this study achieves much higher sensitivity, specificity, and overall accuracy for the presence of penetrating diaphragm injuries than any previously published series using CT in this patient population. In patients in whom the results of CT were validated with operative evaluation, MDCT was more than 90% accurate in either detecting or excluding diaphragmatic injury after penetrating torso trauma. The sensitivity and specificity of MDCT in this highly selected group are somewhat misleading, however, because this subset of the study population has a much higher prevalence of diaphragm injuries than the study group as a whole does and those patients who clearly had no diaphragm injury were not considered. The true sensitivity and specificity of MDCT to detect diaphragm injury is clearly higher than that reported in this subset.

The most diagnostically helpful MDCTs were in patients in whom the tract of penetration could clearly be visualized. A wound tract extending up to the diaphragm was the most useful MDCT finding to identify patients with a potential diaphragmatic injury. This has been noted in other studies, including several from our institution. If noted to be extracavitary, the need for surgical evaluation is precluded. If the tract was remote from the diaphragm, the diagnosis of diaphragmatic injury was similarly excluded. MDCT also allowed for detection of other injuries that required operative intervention when cavitary penetration occurred.

One recent prospective study suggested that all patients with penetrating thoracoabdominal trauma be evaluated with laparoscopy because of the high incidence of diaphragmatic injury and the severe morbidity of missed injuries. Our results indicate that MDCT can safely evaluate many patients with penetrating injuries to the thoracoabdominal region without subjecting them to the risk of anesthesia and morbidity of operative intervention if no injury is seen in the region of the diaphragm. Of the false-negative results in this current study, although no discrete diaphragm injury was noted, all had pathologic findings near the diaphragm, necessitating additional investigation. Despite a high sensitivity and specificity of MDCT to detect or exclude diaphragm injuries after penetrating torso trauma, patients with injury in the proximity of the diaphragm and equivocal findings on MDCT still require additional diagnostic evaluation to definitively exclude diaphragm injury to prevent the morbidity of missed injuries.

This study was designed to describe the clinical effectiveness of MDCT in the detection of diaphragm injuries in patients with penetrating torso injury. The CT reports were retrospectively examined and were not specifically read with intent to detect or exclude diaphragm injury. This is both a strength and limitation of this study. The fact that actual CT reports that would be available to the treating physician were used allows for more realistic evaluation of the practical accuracy of MDCT to detect or exclude diaphragm injury. Additionally, this allowed for blinding of the results, as the findings at surgical evaluation were not considered when the CT reports were generated. However, the fact that the attending radiologists who read these CTs were not targeting their findings at surgical evaluation were not considered when the CT reports were generated. The retrospective nature of this study is clearly a significant limitation. The lack of surgical confirmation of CT findings does not allow for precise determination of true-negatives, and therefore, precludes exact calculation of diagnostic accuracy. Another significant limitation is the number of patients in this study who were lost to long-term follow-up. Clearly, some of those patients who were lost to follow-up may have evidence of missed injury that was not revealed in this limited retrospective study. However, of the patients followed up, there were no missed injuries and no known missed injuries in the entire cohort.

This study demonstrates that MDCT is an accurate test to evaluate the diaphragm after penetrating trauma. MDCT should be a mainstay in the diagnostic evaluation of patients who present after penetrating torso trauma without discrete indications for operative intervention.

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Is Magnetic Resonance Imaging Essential in Clearing the Cervical Spine in Obtunded Patients With Blunt Trauma?

John J. Como, MD, Marsha A. Thompson, RN, James S. Anderson, MD, Rajiv R. Shah, MD, Jeffrey A. Claridge, MD, Charles J. Yowler, MD, and Mark A. Malangoni, MD

Background: The optimal method of clearing the cervical spine (CS) in obtunded blunt trauma patients (OBTPs) remains unclear. Computed tomography (CT) identifies most injuries but may fail to detect ligamentous and spinal cord injuries. Magnetic resonance (MR) imaging has been widely used to exclude these. The purpose of this study was to evaluate whether CT of the CS (CT-CS) alone is adequate to clear the CS in OBTPs. Our hypothesis was that MR imaging of the CS (MR-CS) does not contribute relevant information and is not necessary in this patient population.

Methods: A prospective evaluation of OBTPs with a CT-CS negative for acute trauma and an MR-CS obtained for clearance was performed at a Level I trauma center between July 1, 2004, and June 30, 2006. Data gathered included demographic results of CT-CS and MR-CS, timing of MR-CS, Glasgow Coma Scale score at time of MR-CS, adverse events occurring while obtaining MR-CS, and cervical collar complications.

Results: One hundred and fifteen patients were identified. There were 90 male patients. The mean age was 43.9 years ± 1.9 years, mean Injury Severity Score was 24.4 ± 1.0, and mean length of stay was 23.4 days ± 1.2 days. The MR-CS was performed on hospital day 7.5 ± 0.6 and the mean Glasgow Coma Scale score at the time of MR-CS was 8.3 ± 0.3. Six MR-CS (5.2%) subsequently identified acute injuries. Findings included microtrabecular injuries, intraspinous ligament injuries, a cord signal abnormality, and a cervical epidural hematoma. None of these findings changed management and none required continued cervical collar usage. Six cervical collar complications were identified (5.2%). No adverse events related to transport or obtaining MR-CS occurred. Eliminating MR-CS would have decreased health care costs by over $250,000 during this period.

Conclusions: MR-CS may be unnecessary in the OBTP if the CT-CS is negative. Elimination of MR-CS in this population will lead to earlier removal of cervical collars, decreased cervical collar complications, protection of the patient from exposure to potential risks inherent to obtaining this study, and decreased health care costs.

Key Words: Magnetic resonance imaging, Cervical spine, Obtunded blunt trauma patients.

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expensive and significantly increases hospital costs. Also, transporting an OBTP to an unmonitored and often remote setting such as the MR suite has the potential to expose the patient to multiple risks.

Our hypothesis was that MR-CS is unnecessary in the OBTP if the CT-CS is negative, especially with the newest generation of scanners. Should this hypothesis prove correct, an unnecessary test could be eliminated, leading to decreased cost and reduced patient risk. If CS clearance in this patient population could be based on the results of CT-CS alone, this would lead to earlier removal of cervical collars and thus fewer cervical collar complications.

PATIENTS AND METHODS

All OBTPs admitted to MetroHealth Medical Center, a Level I trauma center in Cleveland, OH, between July 2004 and June 2006 undergoing both CT-CS and MR-CS were included. The MetroHealth Medical Center provides tertiary trauma care for the metropolitan Cleveland area as well as 17 counties in northeastern Ohio. Prospective data were collected on these patients, including age, gender, mechanism of injury, Glasgow Coma Scale score at time of MR imaging, need for a definitive airway, results of CT-CS, results of MR-CS, adverse events during MR image acquisition, intervention on the CS, hospital day of MR-CS, length of hospital stay, and complications caused by the cervical collar. An obtunded patient was defined as a patient who was unable to reliably describe the presence or absence of CS symptoms, in the opinion of the examining physician. Adverse events during MR image acquisition were defined as hemodynamic events that did not allow the study to be completed. Complications caused by the cervical collar were defined as skin breakdown as identified by the skin care team during weekly rounds in our intensive care unit.

All OBTPs underwent CT-CS soon after admission to the hospital. Plain films were not routinely performed in this patient population because of the low incidence of adequate films in OBTPs. Evidence of injury on the CT-CS prompted a spine consultation from either the neurosurgical or the orthopedic service. These patients were excluded from the study. Patients with obvious neurologic deficits received a spine consultation and were excluded from the study. MR-CS was not obtained in these patients unless requested by the spine service to further define the injury. If the CT-CS revealed no evidence of injury and the patient remained in an obtunded state, MR-CS was performed as soon as the patient’s condition allowed for transport to the MR suite. If MR-CS showed evidence of injury, a spine consultation was obtained. If the MR-CS was read as negative, the cervical collar was removed and the patient’s CS was considered cleared. A spine consultation was not obtained in this situation.

Findings of CS injury on CT included fracture line extending on two consecutive cuts involving the bony spinal column, marked (more than the anteroposterior dimension of the vertebral body) prevertebral soft tissue swelling or hematoma, malalignment not explained by degenerative changes, and abnormal facets or posterior malalignment on the sagittal reconstruction. Injuries to the occipital condyle involving the craniocervical junction were included in this definition of CS injury. Findings of CS injury on MR imaging included direct injury to the discoligamentous complex, cord signal abnormality, marrow edema related to microtrabecular injury, and injury to the posterior ligaments or capsular injury to the facets.

CT-CS scans at the home institution (n = 106) were obtained by using a Philips Brilliance Power 16 multislice detector scanner (Philips Medical Systems, Best, The Netherlands). Scanning was performed from the skull base to at least the T1 vertebral body. Sixteen-row detector CT scan was performed using 16 × 0.75 mm collimation with 1-mm interval reconstructions and 0.5-mm overlap. Sagittal and coronal multiplanar reconstruction data sets were performed at 1-mm intervals using the axial data sets. All images were viewed on a Picture Archiving Communication System (PACS, General Electric Medical Systems, Milwaukee, WI) workstation. Axial data sets at 1 mm were also obtained and reviewed with the sagittal and coronal data sets. Bone and soft tissue windows were reviewed by four certificate-of-added-qualification neuroradiologists. All outside scans (n = 9) were obtained using four multislice detector scanners.

MR-CS imaging was performed on a 1.5T Philips Infinion or Eclipse unit with high-resolution CS coil. All MR-CS studies were performed at the home institution. The trauma protocol included sagittal T1, sagittal fast spin-echo, and sagittal short tau inversion recovery sequence with axial gradient echo sequence of the entire CS. Sagittal images routinely depicted up to the upper thoracic spine. Sagittal slice thickness was 3 mm and axial data sets were also obtained at 3 mm.

Data were analyzed using SPSS (Chicago, IL). Continuous variables were described as means ± SEM. Categorical variables were expressed as a fraction and percentage.

The Institutional Review Board at the MetroHealth Medical Center approved the study.

RESULTS

One hundred and fifteen patients were identified. There were 90 male patients (78%). The mean age was 43.9 ± 1.9 years, mean Injury Severity Score was 24.4 ± 1.0, and mean length of stay was 23.4 ± 1.2 days. The MR-CS was performed on hospital day 7.5 ± 0.6 (range, 1–36 days) and the mean Glasgow Coma Scale score at the time of MR-CS was 8.3 ± 0.3. One hundred and ten patients (96%) were dependent on mechanical ventilation at the time of MR-CS. Motor vehicle collisions were the most common mechanism of injury (41%), followed by falls (14%), motorcycle collisions (10%), and assaults (10%). A reliable clinical examination could not be obtained in any of the study subjects secondary to deceased mental status. All patients had a CT-CS read as...
negative for acute injury. One hundred and six of these were performed at the home institution and were performed on a 16-row detector CT scanner, whereas nine were performed at outside institutions on 4-row detector scanners. All patients then underwent MR-CS at our institution as soon as their clinical status permitted.

Six MR-CSs (5.2%) subsequently identified acute injuries or the suggestion of acute injuries (Table 1). Findings included microtrabecular injuries in three patients, intraspinous ligament injuries in two patients, and a minimal capsular injury, a questionable cord signal abnormality, and a cervical epidural hematoma in one patient each. Two of the six patients had more than one finding on MR-CS. Except for the epidural hematoma, these were all minimal findings. None of these findings changed management, and none required continued cervical collar usage. The cervical epidural hematoma, although an important finding, was actually a consequence of an epidural hematoma that ascended from an injury in the thoracic spine. It did not require continued cervical collar immobilization.

Six cervical collar complications were identified (5.2%), all decubitus ulcers. No adverse events related to transport or obtaining MR-CS occurred. Eliminating MR-CS would have decreased health care costs by over $250,000 during this period.

**DISCUSSION**

One of the major challenges that the practitioner providing care for trauma patients encounters regards exclusion of CS injury. The Eastern Association for the Surgery of Trauma has published a set of practice guidelines for identifying CS injuries after trauma. If the patient is awake, alert, and without mental status changes and has no neck pain or tenderness on a full range of motion, no distracting pain, and no neurologic deficits, the patient may be considered to have a stable CS, and cervical immobilization devices may be removed. The situation is considerably more difficult in the obtunded patient. The Eastern Association for the Surgery of Trauma guidelines with regard to this topic, originally published in 1998, stated that the CS would be considered stable if a combination of adequate three-view plain films (with CT supplementation as necessary) and thin-cut axial CT images through C1 and C2 showed normal findings. This guideline was questioned and led to a revision, published in 2000, which in addition to the above, recommended that lateral flexion-extension views of the CS under fluoroscopy with static images obtained at the extremes of flexion and extension be obtained. This practice has been similarly questioned.

Expeditious and appropriate clearing of the CS in OBTPs will permit timely removal of the cervical immobilization device while avoiding missing injuries that require continued immobilization or surgical intervention. The first step in prudent clearance of the CS is excluding abnormalities in alignment, bony structures, cartilaginous elements, or soft tissues. This is generally accomplished with some combination of plain films and CT-CS. In our institution, plain radiographs of the CS have been found to be frequently inadequate. Thus, CT-CS has been obtained in all OBTPs requiring imaging of the CS. The entire CS is visualized from the skull base to at least the level of T1. Focused CT of segments of the CS is not performed at our institution. If these films demonstrate no acute injury, the patient is considered cleared radiographically, and an examination of the CS is attempted to exclude ligamentous injuries that may not be obvious on CT. If these patients demonstrate no tenderness

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**Table 1 Characteristics of Patients With Negative CT-CS Findings and Positive MR-CS Findings**

<table>
<thead>
<tr>
<th>Patient</th>
<th>CT-CS Findings</th>
<th>MR-CS Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>47M</td>
<td>Microtrabecular injury of the occipital condyle on the left. No ligamentous injury seen. Slight increased signal intensity in the C1-C2 articulation and occipital condyle and C1 articulation reflective of minimal capsular injury. Paraspinal muscle injury.</td>
<td>Nonspecific changes in the marrow of the C4, C5, and C6 vertebral bodies, which may reflect degenerative change, but edema related to microtrabecular fracture is not entirely excluded. Small amount of prevertebral soft tissue edema is noted from C4 to the upper thoracic spine. No ligamentous disruption is identified.</td>
</tr>
<tr>
<td>84M</td>
<td>Nonspecific changes in the marrow of the C4, C5, and C6 vertebral bodies, which may reflect degenerative change, but edema related to microtrabecular fracture is not entirely excluded. Small amount of prevertebral soft tissue edema is noted from C4 to the upper thoracic spine. No ligamentous disruption is identified.</td>
<td>Paraspinal edema. There is questionable signal abnormality in the cord seen only on the axial images and not on the sagittal images. It probably reflects technical differences and artifact and not true cord pathology. If the patient’s symptomatology is pertaining to the cord and there is significant discrepancy between clinical finding and MR imaging, a follow-up MR imaging could be obtained to see whether there are any secondary changes in the cord.</td>
</tr>
<tr>
<td>42M</td>
<td>On axial images, note is made of epidural hematoma extending across the cervical spine. This results in mild compression of the thecal sac without any deformity of underlying cord. Within this, in the right parasagittal location, a linear hypointensity is seen on T2-weighted images. This may represent a focal clot. However, possibility of this representing a bone fragment is not excluded.</td>
<td>No evidence of cord injury. No evidence of ligamentous injury. Contusions in the cerebellum and paraspinal edema and hemorrhage as well as interspinous ligament injury.</td>
</tr>
<tr>
<td>49M</td>
<td>No evidence of cord injury. No evidence of ligamentous injury. Contusions in the cerebellum and paraspinal edema and hemorrhage as well as interspinous ligament injury.</td>
<td>Increased signal within the C6-C7 intervertebral disc space seen on STIR imaging, which may represent microtrabecular injury of one of the vertebral bodies. Increased signal seen within the space between the C5 and C6 posterior spinous processes may represent injury to the intraspinous ligament.</td>
</tr>
<tr>
<td>55M</td>
<td>Increased signal within the C6-C7 intervertebral disc space seen on STIR imaging, which may represent microtrabecular injury of one of the vertebral bodies. Increased signal seen within the space between the C5 and C6 posterior spinous processes may represent injury to the intraspinous ligament.</td>
<td>None of the findings changed management, and none required continued cervical collar usage. The cervical epidural hematoma, although an important finding, was actually a consequence of an epidural hematoma that ascended from an injury in the thoracic spine. It did not require continued cervical collar immobilization.</td>
</tr>
</tbody>
</table>

STIR, short tau inversion recovery.
to the CS on full range of motion, they are cleared clinically. Once clearance is accomplished radiographically and clinically, the cervical collar is removed, and all CS precautions are discontinued.

In the OBTP, a reliable physical examination cannot be obtained, and ligamentous injury must still be excluded by an alternate method. One approach is to attempt to wait until the patient’s mental status has cleared sufficiently to permit a reliable physical examination. This approach is not without morbidity because cervical collar use may lead to discomfort, skin maceration and ulceration, and may also limit sites used for central venous access (Fig. 1). Davis et al. reported decubitus ulcers in 44% of obtunded patients with trauma. Cervical collar immobilization in patients with severe head injury may also elicit or exacerbate intracranial hypertension via compromise of jugular venous drainage. It also interferes with normal swallowing mechanisms, which may lead to difficulty clearing secretions and possible aspiration. The presence of the cervical collar and the inability to extend the neck also leads to difficulty when the patients require endotracheal intubation or tracheostomy. Prolonged immobilization is clearly not the optimal management of the CS in the obtunded patient with trauma.

Dynamic fluoroscopy has been advocated by several authors as the best method to clear the CS in OBTPs. This has been shown to be a safe technique if performed properly; however, there has been at least one case of quadriplegia reported when the technique was not performed correctly. Padayachee et al. reported that dynamic fluoroscopy did not identify any patients with cervical fracture or instability not already identified by plain radiographs and fine-cut CT with three-dimensional reconstructions. In addition, Bolinger et al. reported that bedside fluoroscopic flexion and extension studies were considered to be adequate in only 4% of patients. Because this technique adds little information and is commonly inadequate and potentially dangerous, it may not be the optimal way to clear the CS in OBTPs.

At our institution, OBTPs underwent CT-CS followed by MR-CS as soon as the patient was deemed sufficiently stable for transport to the MR suite. MR-CS is costly and its acquisition in injured and perhaps uncooperative patients can prove potentially dangerous. Although no clinically significant adverse events occurred during this study either while transporting the patient or during the MR-CS, the potential for risk is certainly relevant. Adverse events in the MR suite during attempts to clear the CS in OBTPs have in fact occurred in our institution both before the initiation of the study and subsequent to its conclusion. Other disadvantages of MR imaging include the incompatibility of ferrous components with the magnet and the cumbersome and time-consuming nature of the study. Scanning times are often long and the nature of the suite is usually such that nursing personnel cannot be physically close to the patient.

Availability of MR imaging is often restricted on nights and weekends. The MR suite is frequently located in a remote area of the hospital, and transport requires multiple personnel and monitoring equipment to safely immobilize the often critically ill patient (Fig. 2). Although it would be ideal to obtain MR-CS early, because the ability to detect soft tissue injury may diminish after 72 hours, the aforementioned factors often precluded us from being able to do this. However, we are not aware of any injuries that were missed on MR-CS because of this test being performed too late. In
addition, the cost of the MR-CS study itself is more than $2,000 (technical fee of $1,931 and professional fee of $352). Eliminating MR-CS would have decreased health care costs by over $250,000 during the study period. These figures do not include the cost of personnel and equipment needed to transport the patient to the MR suite, which, in our hospital, is a considerable distance from the intensive care unit.

Advantages of MR in the evaluation of the CS include the ability to provide images of the vertebral column, spinal cord, and related soft tissue structures, permitting assessment of ligamentous stability without exposing the patient to the hazards of flexion-extension radiography.\textsuperscript{1,5,7,8,17,18} However, new developments in CT technology, such as multislice or multidetector CT, have made the detection of some soft tissue injuries possible without the need for MR.\textsuperscript{3} It is possible that all clinically relevant injuries may be detected by CT, and that MR will no longer be needed in the screening of the OBTP.\textsuperscript{3} MR-CS would continue to be used to better define injuries detected during CT-CS screening.

MR imaging is considered to be the reference standard for evaluating CS soft tissue injuries.\textsuperscript{3,7,19} MR-CS has been compared with plain radiographs and dynamic fluoroscopy, but rarely to CT-CS. In 2002, the National Emergency X-Radiography Utilization Study (NEXUS) group reported that of 66 blunt trauma patients undergoing both CT-CS and MR-CS, only 12% (3 of 25) of patients with ligamentous injuries identified by MR-CS were detected by CT-CS.\textsuperscript{20} The stability and gravity of the types of injuries missed by CT-CS was not addressed in this study. CT-CS, however, detected all 28 cases of subluxation dislocation, whereas MR-CS missed 2 of these. The conclusion of this study was that in clinical practice, MR imaging was better at identifying soft tissue injuries, whereas CT was more effective at identifying bony injuries. Ligamentous injury, however, may be of limited significance in the absence of subluxation dislocation, and this specific type of injury is detected adequately by CT-CS.

Diaz et al. reported that 1,577 blunt trauma patients at least 15 years old were found to have an unreliable examination because of altered mental status or distracting injury.\textsuperscript{21} Of these, 1,299 (82.4%) had no fractures on both plain films and CT-CS (majority performed on an 8-slice scanner). Eighty-five patients without fractures on plain films or CT-CS underwent MR-CS. Indications for MR-CS in this group were abnormalities on CT-CS (vertebral body or facet joint malalignment or subluxation not explained by degenerative joint disease), neurologic deficits, complaints of pain or tenderness in awake patients, or patients exhibiting persistent decreased level of consciousness. Relevant to this discussion, 22 OBTPs had MR-CSs obtained because they were obtunded. Ten (45%) of these were found to have ligamentous injury. The significance of these injuries, however, is unclear as none of these patients required surgery.

Stassen et al. retrospectively reported on a series of 52 OBTPs who underwent both a CT-CS and an MR-CS during a 12-month period.\textsuperscript{22} Forty-four had a negative CT-CS (defined as no bony injury). Of these, 13 patients (30%) had a MR-CS positive for ligamentous injury. None of these patients required surgical intervention. The stability of the injuries identified by MR-CS was not addressed in the study. It is also unclear whether the ligamentous injuries identified on MR-CS were apparent on CT-CS.

In contrast, Adams et al. retrospectively reviewed 97 trauma patients who had undergone an MR-CS for blunt trauma during the calendar year 2004.\textsuperscript{23} The purpose of the study was to investigate the sensitivity of CT scanning for spinal injuries compared with MR imaging. MR-CS was performed for pain or neurologic deficit in responsive patients and in obtunded patients. Of the 20 OBTPs, it was found that all patients with a negative CT-CS (using a 4-slice CT scanner) also had a negative MR-CS. In this small group of patients, MR-CS added no information when compared with CT-CS.

The largest study to date regarding this problem was published by Hogan and colleagues from Baltimore.\textsuperscript{3} They retrospectively reviewed 366 OBTPs who had undergone MR-CS during a 32-month period. All had previously undergone a CT-CS (using either a 4- or 16-slice scanner) deemed negative for injury. CS injuries included CS fractures, marked prevertebral edema, CS malalignment, widening of the normal interspinous and intervertebral disk spaces, and loss of normal facet coverage. Only 12 MR-CS (3.3%) identified acute injuries. These included ligamentous injuries, cord contusions, and acute intervertebral disk abnormalities. Of the 4 ligamentous injuries elucidated (1.1%), none were unstable. Multidetector row CT had negative predictive values of 98.9% (362 of 366 patients) for ligament injury and 100% (366 of 366 patients) for unstable CS injury.

Our prospective study demonstrates that in a series of 115 consecutive OBTPs who underwent CT-CS negative for trauma and subsequent MR-CS in an attempt to exclude significant CS injury, no significant injuries that required continued CS immobilization were identified. The injuries that were realized on MR-CS and not on CT-CS did not require treatment and would not have benefited from continued cervical immobilization. An epidural hematoma was identified that resolved without active intervention, and this case did not require continued cervical immobilization. The single abnormality of the spinal cord represented an injury in a young man who had attempted hanging and later died secondary to a severe brain injury. It was thought to be an extremely minimal, if even a true, finding. Autopsy revealed no injury to the CS. The ligamentous injuries and microtraumatic injuries that were identified also did not require any additional treatment or further immobilization. These were all stable injuries.

In this study, MR-CS provided no clinically relevant information, and therefore, was not needed. Our present protocol of using MR-CS to clear the CS in OBTPs added cost, exposed the patient to potential risk, and led to complications related to the prolonged use of cervical collars, while provid-
ing no clinically relevant information. Our results have led to a change in our practice with regard to CS clearance in OBTPs. The revised protocol allows us to remove cervical collars in OBTPs after a CT-CS has been confirmed as negative by an attending radiologist. MR-CS will no longer be performed as requisite for spine clearance in this patient population. We are collecting further data on this patient population prospectively to provide additional proof that this is a safe and adequate approach.

Some limitations of this study should be noted. First, these data are only relevant for centers that are using 16-row detector CT, as 92% of our studies were performed on such scanners. Second, we did not have long-term follow-up on our patients. This is very difficult in the trauma population in general, and particularly in the obtunded subset of this group. We, however, know of no adverse events or missed CS injuries resulting from the use of our protocol. Finally, our sample size, although it consists of over 100 patients, is relatively small. The process of accruing patients is slow (just over 1 per week), and obtaining a larger population would take many years. We have demonstrated, however, that in our cohort, 115 consecutive MR-CS studies were performed that added no clinically relevant information. The incidence of significant CS injury in OBTPs with a negative CT-CS is small and approaches zero. Our data suggests that this number is less than 1%; when considering data from other series, it is probably much less than this. When taking into account the risks of MR-CS and realizing the paucity of useful information obtained, it seems prudent to clear the CS based on the results of CT-CS alone.

MR-CS may be unnecessary in the obtunded patient if CT-CS is negative. Elimination of this study will decrease the risk involved in transporting a critically ill patient from the intensive care unit. It will also minimize cost, lead to earlier removal of cervical collars, and decrease cervical collar complications.

REFERENCES

Pregnancy is Not a Sufficient Indicator for Trauma Team Activation

Wendy Greene, MD, Linda Robinson, MA, MS, RN, Anne G. Rizzo, MD, Joseph Sakran, MD, Kimberly Hendershot, MD, Aaron Moore, MD, Kimberly Weatherspoon, BS, and Samir M. Fakhry, MD

**Background:** Trauma complicates 6% to 7% of all pregnancies. Adverse outcomes are rare when monitoring is normal and early warning signs absent. Trauma systems often use pregnancy as the sole criterion (PSC) for partial trauma team activation. This study compares outcomes of pregnant patients presenting with PSC versus other physiologic, mechanistic, or anatomic (OPMA) activation criteria.

**Methods:** Three hundred fifty-two consecutive obstetric partial trauma activation patients (2000–2005) were grouped by length of gestation and evaluated for activation criteria and early maternal and fetal outcomes. Data were analyzed using descriptive statistics and analysis of variance.

**Results:** Patients ranged in age from 16 to 44 (mean age, 28 ± 6.4) and in weeks gestation between 1 and 40 weeks (mean, 25 ± 8 weeks). Eighty-two percent had been in vehicle crashes. One hundred eighty-eight (58%) were activated based on PSC and 137 on OPMA. No PSC patient had injuries sufficient to warrant trauma service admission. Ninety-four percent of all PSCs of <20 weeks were discharged home from the emergency department. There were no maternal mortalities. There were four fetal mortalities; two pregnancies were terminated compromised before the trauma event. No patient in the PSC group required admission to the trauma service. There were seven cases of abruptio (2%) and 18 cases of vaginal bleeding or discharge (6%). No case of vaginal bleeding or abruptio in the first 20 weeks was hypotensive at the scene or on arrival.

**Conclusion:** In this study, pregnancy was not an independent predictor of the need for trauma team activation. Standard OPMA trauma activation criteria apply equally to pregnant and nonpregnant patients. These data provide support for more judicious allocation of scarce trauma systems resources.

**Key Words:** Obstetrics, Trauma, Trauma team activation, Over-triage.


A critical requirement for cost-effective health care delivery is the assignment of the right resources to the right patient at the right time. Trauma systems exist to provide definitive care to multiply injured trauma patients. The American College of Surgeons (ACS) Committee on Trauma (COT) recommends that when a pregnant woman is involved in a trauma event that Emergency Medical Service establish “contact with medical control with consideration of transport to a trauma center or an appropriate resource hospital” as well as engage qualified specialists during the initial evaluation. Recommendations for pregnant trauma patients also include evaluation at a trauma center if possible. Based on these guidelines, many trauma centers include pregnancy among other physiologic, mechanistic, and anatomic (OPMA) criteria for trauma team activation (TTA).

Trauma complicates 7% of all pregnancies and is the leading cause of death in the pregnant patient. In the study center, pregnancy is a pre-existing condition in approximately 3% of all TTAs. Studies have shown that trauma now surpasses obstetrical complications as a cause of fetal and maternal death. Despite this fact, adverse outcomes to fetus or mother are still very rare and are generally related to the severity of the maternal trauma. Several studies have documented the predominance of low Injury Severity Scores (ISSs) in the pregnant trauma patient population but the fear of fetal loss, despite lack of significant maternal injury, persists. The study center had identified a high Emergency Department (ED) discharge rate in this population. More than 90% of pregnant TTA patients were discharged from the ED as opposed to 35% to 45% of nonpregnant trauma patients. The purpose of this study was to compare the characteristics and outcomes of pregnant blunt trauma patients who presented to a Level I trauma center with pregnancy as the sole criterion (PSC) for TTA with patients who presented with OPMA trauma criteria. Specifically, we were interested in determining whether TTA was necessary for patients with PSC.

**Patients and Methods**

This retrospective study analyzed medical records and the trauma registry data of pregnant blunt trauma patients.
Three hundred fifty-two pregnant patients designated as PTTAs between 2000 and 2005 comprised the sample. Patients presented at a mean age of 28 (±6.4), a mean gestation of 25 (±8 weeks), and with a mean ISS of 2.13 (±2.78) (Table 2). Fifty percent of the patients had an ISS of 1 or less, with 75% of patients with an ISS of 2 or less. The majority of the patients presented after the first trimester. The third trimester accounted for 47.7% of the patients (n = 168) and 32.1% were in the second trimester (n = 113). Only 9.1% (n = 32) of the pregnant PTTA patients were in their first trimester. Patients at term represented 4.5% (n = 18).

The most common mechanism of injury was overwhelmingly motor vehicle crashes (MVCs) (95%). Falls accounted for 2.8% and pedestrians struck accounted for 1.5%. More than one-third of the MVCs (36.6%, n = 129) were classified as low speed (<35 mph), 33.5% (n = 118) were high speed (>35 mph), and 4.0% (n = 14) of patients were stopped at the time the crash. Speed data were unavailable for 24.4% (n = 86) of MVCs.

Acute abdominal pain was the most common complaint of all patients at the scene (44.6%, n = 157) followed by low back pain (26.7%, n = 97). Despite the frequency of reported abdominal pain, only 36% (n = 92) of patients experienced contractions during their trauma encounter. Ninety-seven percent of these patients were 20 weeks’ or greater gestation. They were split evenly between those whose contractions lasted <4 hours from admission (2.5%, n = 44) and those lasting >4 hours from admission (13.9%, n = 49). Eighteen patients (5.4%) were discharged from the hospital having contractions. Pregnancy outcome was available on those patients who delivered at the study hospital either during the trauma-related hospitalization or during a subsequent obstetrics-related hospitalization. Live births were reported for 82.7% (291) of the patients with 1.1% (4) fetal mortality. Outcome
of the gestation was unknown for 16.2% (n = 57) of the patients.

All but 14 cases provided data on criteria used for PTTA. Fifty-eight percent (n = 197) of obstetric PTTAs were activated on the basis of PSC and 42% (n = 142) were activated on OPMA criteria. Thirteen charts did not provide enough information to determine PTTA criteria.

Outcomes of PSC Versus OPMA

There was no statistically significant difference in any subgroup with respect to maternal age. None of the patients in the PSC group had injuries sufficient for admission to the trauma service; however, eight women who were 20 weeks' gestation or greater were admitted to the obstetric (OB) service. All the patients who were PSC and <20 weeks' gestation were discharged home directly from the ED after obstetric consultation and testing. Three of four known fetal deaths occurred in the OPMA group. One case had oligohydramnios and prehospital fetal compromise (17 weeks). The second was an ectopic pregnancy (6 weeks) and the third followed a dilation and curettage after premature rupture of membranes (14 weeks). The PTTA criteria for the fourth fetal death at 33 weeks could not be determined from the data available. This patient proved to have no significant injuries. An emergency Cesarean section was performed for fetal heart decelerations and resuscitation proved unsuccessful. There were no maternal mortalities (Table 3).

Sixty-three percent of PSCs who were in the first 20 weeks of pregnancy complained of acute abdominal pain or cramping at the scene of the trauma and 27% complained of low back pain. Contractions were documented during the hospital encounter in 10% (n = 2) of the PSC patients before 20 weeks in contrast to 32% (n = 49) of PSCs between 20 and 37 weeks, and 66.6% (n = 6) of those at term. Of those patients with contractions, five were admitted, all to the OB service.

The study cohort had four (1.1%) diagnosed abruptions by pathology specimen, three (0.9%) by ultrasound. Twenty-nine

Table 3 Outcomes by Gestation and Partial Trauma Team Activation Criteria Category

<table>
<thead>
<tr>
<th></th>
<th>&lt;20 wk</th>
<th>OPMA</th>
<th>&gt;20 wk</th>
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<td>Contractions during encounter</td>
<td>2</td>
<td>1</td>
<td>55</td>
<td>33</td>
<td>93</td>
</tr>
<tr>
<td>N reporting</td>
<td>20</td>
<td>33</td>
<td>126</td>
<td>72</td>
<td>251</td>
</tr>
<tr>
<td>With contractions (%)</td>
<td>10</td>
<td>3</td>
<td>43.7</td>
<td>45.8</td>
<td>37</td>
</tr>
</tbody>
</table>

Two patients at 20+ weeks’ gestation admitted to OB service: PTTA criteria unknown.
* One additional fetal demise occurred after 20 weeks’ gestation: PTTA criteria unknown.
† One patient at 7 weeks’ gestation was admitted to trauma service for 4 days: PTTA criteria unknown.
PSC, pregnancy as the sole criteria; OPMA, other physiologic, mechanism, or anatomic criteria; OR, operating room.
patients (8.2%) had positive Kleihauer-Betke (K-B) tests thought to be suggestive of abruption. One abruption, followed for 6 months after a low-speed MVC at 14 weeks, underwent a normal vaginal delivery at term. There were 18 (6%) cases of vaginal bleeding or discharge. Of the six in the <20-week group, two were admitted. Of the 12 in the 20- to 37-week group, five were admitted. No patient with abduction or vaginal bleeding in the first 20 weeks was hypotensive at the scene or on arrival to the trauma bay. There were no cases of vaginal bleeding in the PSC group before 12 weeks and only two cases before 20 weeks (13 and 14 weeks). In one of these cases, a placenta previa had been diagnosed 2 weeks before the trauma. The fetal outcome of both cases is unknown.

**DISCUSSION**

This study evaluated the characteristics and outcomes of all pregnant trauma patients meeting the criteria for PTTA at a large, suburban Level I trauma center. Ninety-five percent of pregnant patients designated as PTTA with PSC were discharged from the ED either directly or after 4 hours of obstetrical monitoring. PSC patients who required admission were all admitted to the OB service. All OPMA patients requiring admission were admitted to the trauma service regardless of gestation. The important discriminator for admission to the trauma service appeared to be the OPMA criteria. Pregnancy in the absence of OPMA criteria seemed to be a prehospital incentive to TTA but rarely predicted the need for the advanced resources that a trauma team provides. Based on the study center’s current TTA criteria, no activations should have occurred in the PSC group for those in the first 3 months of gestation. It is possible, however, that maternal complaints of acute abdominal or back pain or both tipped the balance toward TTA. Further, the existence of a specific PSC designation may encourage activation for pregnancy when not warranted by OPMA criteria.

In 1992, Fildes identified trauma as the leading cause of maternal death and subsequent fetal demise. Trauma was the cause of death in 46.3% of the maternal deaths reviewed compared with maternal causes accounting for 19% of deaths. No maternal mortality occurred in the present study in either the PSC or OPMA groups. There were no cases of fetal demise in the PSC group of patients. Three fetal deaths in the OPMA group occurred in mothers at 20 weeks of gestation or less. Although they occurred in the OPMA group and would generally involve TTA, these fetal deaths are unlikely to have been prevented by the availability of the trauma team. In view of these findings, it is difficult to justify the allocation of the resources that the trauma team represents for the care of a PSC cohort with no maternal or fetal mortality and in which there was no need to admit patients to the trauma service. The few patients with PSC who did require admission (<5%) were admitted to the OB service.

Placental abruption is one of the most feared complications of maternal trauma. In the present study it accounted for one of four fetal deaths. Our cohort universally underwent external fetal monitoring (EFM) for all pregnancies >20 weeks. Previous studies have shown that abruption is a very difficult diagnosis to establish; it can occur at a rate of 2% to 4% with even minor trauma and up to 50% with major trauma. Towery evaluated the usefulness of ultrasonography (US), EFM, and the K-B test for the detection of fetal and obstetric complications after trauma. EFM and US proved most useful, identifying all complications within the first 6 hours of the patient’s hospitalization. However, found that US was <50% accurate and therefore recommended EFM as a more reliable assessment tool for fetal distress secondary to abruption. Ananth found that abruption may be a chronic process with increased risk late in pregnancy secondary to the inelasticity of the placenta at that time. In a study of 80 pregnant trauma patients, Theodorou et al. demonstrated that hemodynamic parameters were poor predictors of fetal loss. They also showed that although moderate to severe injury (measured by ISS >9) was associated with fetal loss, even minor injuries can have the same outcome. In a similar analysis of 62 patients, Baerga-Varela et al. found that maternal hypotension and fetal heart rate were the most reliable potential predictors of fetal well-being and outcome after trauma. In their study, fetal-neonatal death did not correlate with severity of maternal injury. These data suggest that even after minor trauma, there should be a high index of suspicion for abruption. Cardiotography should be initiated upon arrival (not after the trauma evaluation is competed) and continued for 4 to 6 hours. If contractions occur, monitoring should be continued for a minimum of 24 hours. Despite these data, there appears to be an incomplete application of the concepts of early institution of EFM in the ED among a large proportion of programs surveyed by Kolb et al.

Patients who present with PSC after trauma may be best managed by expeditious evaluation by an emergency physician in the ED with rapid referral to the OB service for fetal heart monitoring and ultrasonography. In this model, the trauma team would not be involved with the vast majority of patients whose only indication for TTA is their pregnancy. The trauma team could still respond as indicated when major injuries are identified or deterioration occurs. Our data suggest that such involvement is likely to be exceedingly uncommon in patients with PSC. The available data suggest that immediate access to OB expertise and EFM is a higher priority for patients with PSC than TTA.

In the present study, 95% of pregnant patients with PSC requiring PTTA were discharged home within 4 hours of arrival to the trauma center. The ACS COT guidelines for ED discharge rates after trauma range from 25% to 50%. Our finding of 95% discharges is suggestive of over-triage with respect to TTA in this population. This should not be interpreted to mean that patients who present with PSC are not at risk for maternal and fetal complications. Rather, these patients may be better served by the early availability of OB and neonatal expertise than by the presence of a trauma team. The
OB and neonatal specialists may be better prepared to address the maternal and fetal consequences of what would, in a nonpregnant patient, be a minor injury.

This study is limited by the relatively small sample size and the retrospective nature of chart review. Additionally, complete data on outcome of pregnancy and fetal complications were not available on all patients.

**CONCLUSION**

In conclusion, these data suggest that pregnancy as a sole criterion for PTTA results in significant over-triage and the potential to misdirect scarce and expensive resources. OPMA criteria are more reliable indicators of injury requiring TTA and should continue to be used regardless of the presence or absence of a pregnancy. In busy trauma centers, a more efficient model for trauma patients with PSC would be expeditious evaluation by Emergency Medicine and Obstetrics including the use of US and EFM. The trauma team should remain readily available for consultation if needed.

**REFERENCES**


**DISCUSSION**

Dr. Edward Cornwell (Baltimore, Maryland): As we evolve in our discussions regarding the role and responsibilities of the acute care surgeon, it’s clear that there is an increasing likelihood that trauma surgeons will be in a position of dual responsibility, covering acutely ill surgical patients at the same time that they’re on call to care for injured patients.

Accordingly, it’s appropriate to revisit the criteria for trauma team activation and the resultant rates of overtriage and undertriage. The latest Resources for Optimal Care, 2006, the green book, developed by the Committee on Trauma, suggests that, depending on definitions, a broad range of acceptable triage rates may be appropriate, 1% to 5% for undertriage and 25% to 50% for overtriage.

Against this backdrop, Dr. Greene and associates present this well-written and well-presented study, suggesting there’s an overutilization of finite resources when pregnancy is used as a sole criterion for trauma team activation.

This study of about 340 patients during a 5.5-year period in June of 2005 found that none of the 188 patients, 58% of the study group, who were evaluated based on pregnancy alone, required admission to the trauma service.

Although this registry-based study follows most patients only to discharge, the authors do make a compelling case when one considers the predominance of low injury severity scores and clinical and hemodynamic stability of the pregnancy as the sole criterion (PSC) group.

I have a few questions for the authors. In this study, pregnancy was an indication for partial trauma team activation. Exactly who responded to this activation and is the response different during the nighttime hours as opposed to the daytime hours?

Two, you make a compelling case for reconsidering the criteria for trauma team activation, as none of the 188 PSC patients had injuries sufficient for admission to the trauma service. At the same time, however, even less than 4% required admission to the obstetrics service, including no patients at less than 20-weeks gestation.

Allow me to take a slightly mischievous devil’s advocate position and ask, might we not see our colleagues in another specialty produce a similar article entitled “Pregnancy as the sole criterion is not a sufficient indicator for obstetric team activation”?

When you state that, as you do in the article, “all of the patients who were PSC and less than 20-weeks gestation were discharged home directly from the emergency department after obstetric consultation and testing”, you appear willing to offer the services of the obstetrics consultant to rule out injury
to the fetus, but not the trauma consultant to rule out injury to the mother. How would you feel about a mandatory trauma consultation that falls short of immediate trauma team activation?

In summary, these days of increased scrutiny of resource utilization, combined with the increased clinical responsibilities of the acute care surgeon, require a careful analysis of our quest to assign the right resources to the right patient at the right time.

Dr. Wendy Greene (Falls Church, Virginia): In regard to the first question, the composition of the trauma team, it is composed of a trauma surgeon, resident, an emergency department physician, emergency department nurse, the obstetrician on call, and the obstetrical nurse with the external fetal monitor, which is key.

In regard to the mischievous question as to is pregnancy a sufficient indicator for obstetrical activation, this could be written. However, the obstetrical literature is very clear on the need for obstetrical monitoring, external fetal monitoring, and evaluation of these patients, the reason being that maternal injury is a very poor indicator, whether a severe or mild injury, to determine whether there is fetal distress.

The best determinants at this point in time are the external fetal monitoring in conjunction with an adequate obstetrician evaluation. In regard to the last question, as to whether the trauma service should be included as mandatory in evaluation of obstetrical patients, it will depend on your center and your comfort level with your emergency department physicians.

At Inova Regional Trauma Center, we have a great appreciation and respect for our emergency department physicians and their analyses of patients. They often triage minor trauma patients without having a trauma consult and so it would be dependent upon the institution and your comfort level.

Dr. Robert D. Barraco (Allentown, Pennsylvania): There were three cesarean sections in the 20 to 27-week group with pregnancy alone as sole criterion. Can you comment on what those cesarean sections were and a comment on that would be my fear that cesarean sections may be further delayed or missed, should there be a reduced response. I would be anxious for a prospective look at a rapid response team that may include a mandatory trauma consult to make sure that these cesarean sections did not get missed.

Dr. Wendy Greene: As we know, the cesarean section rate is dependent not only on the variability of whether there’s fetal distress, but there’s also factors of fetal dystocia if the baby is too large to pass through vaginal canal or if there’s infectious complications that would lead to a cesarean section or if the person is past term and requiring a cesarean section.

As far as the obstetrical team being delayed and cesarean sections being delayed as a result of trauma evaluation of the patient, we hope that the obstetrical rapid response team would be able to come in sooner and not be delayed in their evaluation of the patient, since the trauma surgeon is not the one who will be performing the cesarean section. We would like to have the person who will be performing the procedure at the bedside in the most rapid fashion.
The Use of “War Games” to Evaluate Performance of Students and Residents in Basic Clinical Scenarios: A Disturbing Analysis

Jeffrey S. Young, MD, Joseph E. DuBose, MD, Traci L. Hedrick, MD, Mark R. Conaway, PhD, and Barbara Nolley, BA

Background: “Failure to Rescue” is a term applied to clinical issues that, if unrecognized or improperly treated, lead to adverse outcomes. We examined the cognitive components of rescue through the use of a “War Games” simulator format. Our hypothesis was that junior and senior medical students would be less able than interns and residents to detail the actions needed to assess, intervene, and stabilize patients.

Methods: Medical students and residents rotating on the trauma and surgical intensive care unit service participated. Twelve scenarios were created to focus on basic floor emergencies. Scores were assigned for clinical actions ordered. The scenarios were validated by two critical care attending physicians, and these scores were used as the expert group. Scores were assigned by two examiners, and the average of the grades in each area was used. The scores are a ratio of actual to possible correct responses in each section, and in the entire exercise.

Results: Subjects were divided into third-year medical students (MS3), fourth-year students (MS4), first-year residents (PGY1), residents beyond their first year (PGY2+), and experts. There were 20 subjects and 5 experts (n = 85) in each group for a total of 140 simulated cases examined. On initial evaluation, MS4 and PGY2+ performed significantly worse than expert, and MS3 and PGY1 performed similarly to experts. On secondary evaluation, all groups performed significantly worse than the expert group. In determining the diagnosis, only MS3 differed significantly from the experts. On follow-up, and in total score, all performed significantly worse than the experts.

Discussion: All groups had significant deficits in cognitive performance compared with experts in the areas of secondary evaluation, follow-up of the presenting problem, and total performance in simple clinical scenarios. We must design educational systems that rapidly enhance the cognitive performance of students and residents before they are left to independently diagnose and intervene in life-threatening clinical situations.

Key Words: Simulation, Surgical education, Failure to rescue, Resuscitation, Education.

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The introduction of work-hour limitations has prompted many training programs to begin to evaluate the education and competence of trainees in more exacting ways. The previous process of massive patient responsibility, coupled with extended hours in the hospital and minimal cross-coverage, has given way to shift work, night float, limited numbers of admissions to each service, and vastly increased numbers of patient handoffs. In this new environment, the ability of the clinician to rapidly assess and intervene in a situation, with little previous knowledge, is becoming more important. In addition, the ability of junior clinicians to realize that they are in a complex clinical situation and to call for help is of increased importance because most facilities have consolidated their in-house backup such that fewer senior clinicians are covering larger populations of patients.

The 80-hour workweek can decrease the number of complex cases a resident will see by 40%, and decrease the percentage of cases they are able to follow through to discharge by 56%. Although previous studies have not demonstrated a difference in outcomes stemming from this finding, a drop in experience in the late years of medical school and early years of residency may have a significant effect, because these are the periods in which clinicians begin learning how to make independent clinical decisions. Simulation is a hopeful remedy for decreased clinical experience. Simulation can assess and increase resident competency in a controlled environment. As stated by Hammond, “simulation is particularly well suited to critical care and trauma. The nature of these areas created a poor context for learning in real-life situations because of the uncertainty of the process and the patients’ response, the complexity of the problem and possible confounding variables and simultaneous processes, time pressure, and stress. Little didactic teaching takes place in the midst of a crisis and in an emergency, the student or learner is often moved to the observer role, as the instructor or more experienced clinician takes over.”

One major problem with simulation is the difficulty in proving that simulated learning improves the efficiency and
performance of trainees. Kirwin and colleagues examined methods of examining decision making in clinicians. They found great difficulty in separating the judge from the participant in these studies, and thought that standardization of vignettes and grading were necessary for accurate evaluation. Thus, we used this background work to separate our simulation from teaching rounds where cases are developed spontaneously and no consistent grading scheme is available. The majority of situational clinician evaluation and education at present depends on the teaching rounds format, which as we have stated is of variable quality, and has little capability for consistent assessment. In addition, because we do not require clinicians to document their decision-making processes, and because there are checks and balances in any hospital system (experienced nurses, respiratory therapists, pharmacists), routine medical student and resident evaluations may be unable to diagnose significant defects in cognitive performance of trainees until it is too late.

Our previous study demonstrated quantitative and qualitative differences in the decision making of novice clinicians in critical care simulations. This study reaffirmed the work of Patel and colleagues in an additional population of clinicians (emergency medicine and surgery residents). Educators have used low-intensity (table-top, verbal with minimal high-tech features) simulation in the key features examination of Canadian medical students. These and other investigators have found that novices must develop “tools” or “roadmaps” to handle different clinical situations because performance in specific clinical problems does translate well into performance in problems concerning other organ systems.

The purpose of our “war game” simulations is to provide an educational and evaluative tool that will allow us to measure subject performance across a wide range of clinical situations, gauge improvement, and provide the subjects with tools to improve their performance in similar situations in the hospital. Klein and colleagues, in studies of firefighters and small-unit military commanders, found that “deliberate practice” was an essential component to gaining effective experience. “Deliberate practice” involves using the mental processes that would be needed in the real-life situation, in simulation. Therefore, deliberate practice requires in a patient in respiratory distress, asking a trainee, “what would you do next?”, and not asking “what is the differential diagnosis of respiratory distress” because the latter has been shown to be absent from the mental processes of experts in clinical care.

The sessions consist of table-top scenarios of common, high-risk, clinical scenarios of increasing complexity and subtlety. However, the cases examined in this study are the simplest in our simulations (level 1) entailing straightforward clinical problems, presenting in obvious ways, with simple treatments required. The sessions are conducted by an examiner and groups of 5 to 10 students and residents. Naïve participants (no previous experience in “war games”) are always the first to be examined. All participants begin with level 1 cases (Table 1), and are evaluated using a grading template (Table 2).

The purpose of this study was to evaluate the performance of naïve subjects at different levels of training in basic high-risk clinical situations using our “war games” format. Our hypothesis was that there would be steady progression in performance from third-year medical students to junior residents, and that performance would mirror that of experts at the mid-PGY1 and PGY2 levels.

**PATIENTS AND METHODS**

The Institutional Review Board for Social and Behavioral Sciences of the University of Virginia approved the study. The “war games” sessions were conducted twice a week for 1 hour. Students and residents of all levels on the trauma and surgical critical care services were required to attend the sessions in accordance with 80-hour work week rules. After the completion of their rotations, the residents and students were sent electronic mail asking if they would agree to have their de-identified responses used in our research. If the response was “no”, or if they did not respond after two mailings, their responses were deleted from the database.

**Conduct of Sessions**

In our cognitive research laboratory, we have 10 positions for subjects in the “war games” sessions. Microphones are placed at each station, and these are routed to a Dell XPS computer (Dell Computers, Round Rock, TX). A digital transcription program (Express Dictate, NCH Swift Sound, Sydney, Australia) is used to record all audio input and prepare it for transcription.

Subjects are asked to sign in and provide the following data: name, year of residency or medical school, number of weeks completed in intensive care unit, and number of previous “war games” sessions completed. These responses are recorded in the database. A list is provided by the research assistant of all previous cases completed by each subject to assure that they will always receive a different case at each session. naïve subjects are always tested first, with the most junior subject beginning the session. We then proceed.
through subjects from most junior to most senior. Although other subjects can hear the responses of others, the least experienced (lowest training level) naive subject always is tested first. No critiquing or teaching is done until all naive subjects have completed a case.

**Cases**

Three levels of cases are used in the sessions. Level 1 cases consist of basic floor situations including the clinical conditions listed in Table 1. In these cases, the subject is given a “stem”, which is the phone call from the nurse on the floor. The subject is then told to proceed as if he or she was the physician on call for this patient. A grading template (Table 2) is used by the laboratory assistant and the investigator to grade the responses in real time. The transcripts are used in case of discrepancy in grading. The grading template includes laboratory, physical examination, and study results for each case. These data will only be presented if requested by the subject. The case proceeds until the subject has no further orders or action. No immediate debriefing is given so that other subjects are not “taught” during the session. After the completion of cases for all subjects, naive subjects are given a presentation consisting of 36 slides on suggested strategies for the care of these types of patients.

**Analysis**

Five experts (3 emergency medicine/critical care attending physicians, and 2 pulmonary/critical care fellows) were separately presented with all level 1 cases during a single session. Their responses were graded in the usual fashion and used as our validation.

Each grading sheet contains scores in four sections: initial evaluation, secondary evaluation, diagnosis, and follow-up. The scores for each section and a total score are recorded. The possible scores for each section and for the entire case are recorded, and the individual’s performance is expressed as a percentage of possible correct responses in each section and for the problem as a whole.

**Statistical Analysis**

The analysis of variance was used to compare groups of subjects with each other and with the expert performance. A p value of <0.05 was considered significant. This statistical strategy was reviewed with the chair of the division of biostatistics within our Department of Public Health Sciences (M.R.C.). The statistician whom we engaged thought that as long as the groups could be separated by distinct features (year of medical training, number of sessions completed), this statistical analysis was completely appropriate.

**RESULTS**

Eighty naive subjects and five experts were evaluated for a total of 85 subjects. Each expert performed in 12 cases, and there were a total of 140 cases examined in the study.

The groups were separated by level of training, MS3 (third-year medical students), MS4 (fourth-year medical students), PGY1 (first-year residents), and PGY2+ (residents beyond their first year). There were 20 subjects in each trainee group and five clinicians in the expert group.

**Initial Evaluation**

This area consisted of actions such as going to see the patient, performing a physical examination, gathering data from the chart, and evaluating and correcting problems in airway breathing and circulation. MS4 performance differed significantly from expert and from intern performance, and PGY2+ performance differed significantly from expert (Fig. 1).
Secondary Evaluation

This area consisted of ordering actions based on findings in the initial evaluation (laboratory evaluations, X-ray examinations, fluid boluses, etc.). In this area, the performance of all groups differed significantly from that of the experts (Fig. 2).

Diagnosis

Although this study focused more on the subject’s ability to evaluate high-risk conditions and intervene appropriately, the examiner asked the subject “what do you believe is going on?” after the subject completed their secondary evaluation and received the results of the laboratory tests and studies they ordered. In this area, only MS3 performance differed significantly from expert (Fig. 3).

Follow-Up

This area consisted of vital actions in the efficiency of patient care. These included detailing that the subject would reevaluate the patient because their condition had not completely stabilized, ordering a critical care bed, ordering appropriate consults (neurosurgery or neurology for an obvious stroke, cardiology for a confirmed myocardial infarction, etc.), and contacting the senior resident or attending physician to inform them of the events that had transpired. The residents and students performed universally poorly in this area, and all scores were significantly different from the experts (Fig. 4).

Total Score

The composite of all subsection scores was tallied. All groups differed significantly from expert performance (Fig. 5).

DISCUSSION

Surgical education must include changes in response to political and economic pressures. Decreased work hours, increased cross coverage, and the increased use of nonphysician providers all require a better assessment of the true clinical competence of our trainees. Before this point in time, competence was granted by turns of the calendar. When a trainee progressed from the third year of medical school, through senior residency, additional responsibilities were conferred with only minimal attempts to quantitatively assess the ability of that trainee to accomplish these new responsibilities.

We have endeavored to create a simulation system that allows us to quantify the performance of subjects in multiple cases covering many organ systems. Instead of structuring our simulation similar to oral examinations (where the subject is pushed to the limits of their cognitive abilities), we strive to use the simulation to assess, and then, if needed, impose a structured, safe process for patient care in high-risk situa-
tions. In addition, our lowest complexity scenarios (which were used in this study) are straightforward, and competence in these scenarios would be expected by any clinician left to care for patients independently.

The use of simulation in medical education is not novel. Investigators have found that students and trainees at different levels of expertise use knowledge in different ways and reason differently. Our own initial studies confirmed this in surgery and emergency residents, and found distinct operational styles in residents with increased critical care experience.

The importance of cognitive performance in clinicians cannot be underestimated. The Institute of Medicine study in 1999 found that a significant proportion of medical errors focused on decisions and not technical issues. There has been an increase in the volume of scientific work examining the use of simulators in training health-care workers. These studies have demonstrated that participants in simulation programs feel more confident and perform better when tested on the same or different simulations at a future date. However, obtaining more quantifiable measures of improved cognitive performance has been elusive.

We created a system of simulation of low fidelity (low cost) and high reproducibility that allows us to examine isolated aspects of clinical performance (initial evaluation, secondary evaluation, diagnosis, etc.), and to compare improvement in performance with time and multiple sessions. The first step in this study is to evaluate the baseline performance of medical students, residents, and “experts” in this model. What we found is disturbing.

The level 1 cases are by any measure simple. By going to see the patient, intubating patients who are either apneic or severely dyspneic, examining their heart and lungs, completing the evaluation of the patient’s airway, breathing, and circulation (ABCs), and ordering a chest X-ray examination and some baseline laboratory examinations, the subject should score more than 70% on initial examination, and more than 60% overall. Less than 25% of naive subjects in this study, no matter the medical school year or postgraduate level, performed at or above this level. What does this indicate?

The first criticism would be that the simulation is a contrivance with no relation to actual clinical care. If that were the case, we would expect that the experts, who had never seen a “war games” session or transcript, would perform similarly. However, in the 48 level 1 cases presented to the experts, they scored >70% in initial evaluation in >80% of their cases, and >60% in total score in 22 (92%) of them (and in those where they did not, only missed this goal by 1%–2%). The average performance for the experts was 72% in initial evaluation and 71% overall, where the overall performance in all other naive subjects was 55% in initial evaluation and 45% overall. We do not think these results would
have occurred unless expert clinical knowledge translated to expert performance in the simulations. Also, because the experts had never seen a session or grading sheet, it is unlikely they knew how to “game” the scoring in any way. In addition, the expert sessions were not conducted by the principle investigator (J.Y.), but by three separate chief residents on the trauma service who had conducted at least 10 “war game” sessions under supervision. This was done to ensure that no hints were given to the experts to improve their scores.

Second, it is possible that we are testing knowledge that is not essential to medical students and junior residents. I would ask the reader to examine the grading sheet in Table 2 to evaluate this criticism. As can be seen, there are points awarded for items that not all senior clinicians would agree are important, but that is why we do not expect perfect performance. These controversial items are part of our additional goals to enhance the medical students’ and junior residents’ performance in these areas by giving them a general set of laboratory tests and studies that can be ordered routinely in patients where the initial evaluation reveals a serious medical emergency requiring urgent evaluation. We think that any controversy about individual items would not contravene the findings of poor performance in the simplest patient care measures.

The third criticism would be that we are not evaluating true differences because of the contamination of subjects during the group sessions. As we have stated, sessions are conducted in groups, and a critique of this process could be that the naive subjects could benefit from the mistakes and performance of the subjects preceding them. We have tried to control this as best we can, and there are practical issues involved. First, no critique or discussion is performed within the group until all the naive subjects have performed. Second, this is an educational offering as well as a research project, thus we thought that we had to maximize the exposure of students and residents to the process. Individual sessions are not practical, and we thought that the group dynamic (being concerned about your performance in front of others) at least in a small way creates an apprehension that could equate with having to make these decisions alone in the middle of the night in the hospital. Third, we audited the performance in the naive and one-session groups with time. We plan on a future publication describing the overall increase in performance of naive subjects during the years of the project, but within defined time frames, there were still significant differences between first-time and second-time participants (naive overall score 0.45 ± 0.12 vs. performance after one session 0.54 ± 0.14, p < 0.002 for participants of all levels). Thus, we think that, despite the fact that the sessions are conducted in groups, we are able to detect significant differences between groups.

Fig. 3. Performance of individual groups in choosing the correct diagnosis of the patient in the simulation. *p < 0.05 versus expert group.
The third conclusion from this study is the one we think is correct: we are not teaching medical students and junior residents a cognitive framework to function in these situations. It seems that this framework is created with time and experience (experts), but this does not help the patient with shortness of breath evaluated by an intern on August 5 at one in the morning. Only by beginning to simulate these situations, testing performance, and creating a framework in the trainees for how to think in these situations, can we hope to improve patient safety in these situations. We also should accept that backup (in the age of restricted work hours) is not always instantly available and even if it was, the person at the bedside must have a process of care in mind that tells them when to call for help. We found that the points for calling for backup were the most often missed in the naive subjects. Although this may be a contrivance of the simulation, it was not often missed by the experts.

A potential critique of the study is the “poor” performance of the experts. If the sample grading sheet is examined, there are essential components of care (establishing an airway, etc.) and less important items (ordering a troponin value, follow-up chest radiograph, etc.). When we examine the grading in the most essential components, we see that the expert scored far higher than the other groups in these areas. Why did they not score 100%? We would put forward that if they had done that, the grading tool would be suspect. There are tremendous individual variations in care and priorities, and we were testing these skills with a very broad tool. You might expect a long-term Advanced Trauma Life Support instructor to score 100% on the practical portion of that course, but I would put forward (especially for myself) that small variations in style that creep into the mental models of clinical care begin to deviate from “classic” answers, and as expertise develops, more leeway would develop in mental processes, thus decreasing “measured” performance. We think a fairer way to look at the results is in comparison with the other groups and not in comparison with a standard of 100% performance. We could easily change the grading scheme to create much higher percentage correct by heavily weighing “classic” components of care (airway, breathing, and circulation), but we think that would hinder our ability to dissect into those areas that require educational reform.

Another potential criticism is the relevance of this study with regard to actual bedside care. Are we making better bedside practitioners? Although some authors have attempted to evaluate the effect of training on bedside performance,26,27 these studies have looked at very defined clinical steps (basic steps in trauma resuscitation, and airway management). Other
attempts to measure the effect on bedside care have focused on surveys of resident “feelings” toward these situations (did the training make them more “confident”), but made no attempt to see if there was an effect on the actual care that was delivered. Evaluating the effects of educational techniques on clinical care is the “holy grail” of education research. As others have shown, the complexity of modern-day hospital medicine, with the layers of care provided by nurses, pharmacists, and others prevents the discovery of many poor medical decisions that are not translated into poor care that can be objectively measured. Also, many instances of suboptimal care are the results of system failure, and not individual decisions. Thus, we have chosen to study this educational process in our laboratory, instead of expending a great deal of effort to measure its effect in the clinical setting. We do have feedback from participants, indicating that they enjoyed the sessions, felt more confident after the sessions, and wished they were more broadly available. However, we do not see the scientific usefulness of these informal surveys, other than to provide a useful check on the attitudes of the subjects toward the sessions. We submit that the well-documented difficulty in evaluating the effect of educational processes on clinical care should not inhibit this research.

Advanced cardiac and trauma life support courses that are often provided for interns may have some beneficial effect, but these courses do not focus on the areas we are testing in these simulations. We think that the simulations we test are more likely to be encountered by a medical student or resident by themselves and require independent decision making. A cardiac arrest or multiple trauma situations will almost always have team mobilization, and thus, less will be required of the student or junior resident.

We will continue to use the “war games” simulations to evaluate and enhance the cognitive performance of students and residents. Future studies from our group will evaluate the ability of multiple “war games” sessions to improve overall performance, and if this simulation system can change the overall performance of students and residents through diffusion of the principles beyond those who participate directly in the sessions.

Fig. 5. Performance of individual groups in total tasks required in the evaluation and treatment of the simulated patient. *p < 0.05 versus expert.

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Histidine Inhibits the Degradation of Cells Suspended in Ringer’s Lactate

Cuthbert O. Simpkins, MD, Viktoria Ekshyyan, MS, and Brad Snyder, MD

Background: We previously demonstrated that the degradation of a suspension of Jurkat cells in Ringer’s lactate (RL) was inhibited by the addition of a 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid/Tris buffer. Given the ability of histidine to buffer protons in the physiologic range (pKa = 6.0), we hypothesized that this amino acid would have the same effect.

Methods: RL was made in our laboratory using sodium 1-lactate. Jurkat cells were suspended in RL alone or RL with various concentrations of histidine or other test reagents at 37°C for 4 hours or 24 hours in an atmosphere of 95% air and 5% CO2. Using flow cytometry, we measured cell shrinkage, phosphatidylserine translocation, propidium iodide uptake, and intracellular oxygen free radical production.

Results: Cell shrinkage was induced by suspension in RL after 4 hours incubation. At 4 hours, cell shrinkage was inhibited by all concentrations of histidine tested, 7.8 μmol/L to 10 mmol/L. There was no statistical difference between cells suspended in medium and cells suspended in 1 mmol/L or 10 mmol/L histidine. After 24 hours incubation, 100% of the cells in RL had undergone cell shrinkage whereas in 10 mmol/L histidine only a mean of 20% of the cells had undergone cell shrinkage. The inhibitory effect of 1 mmol/L histidine at pH 7.4 was compared with that at pH 6.8. After 4 hours incubation, there was no difference. After 24 hours incubation, the inhibitory effect at pH 7.4 was significantly greater than that at pH 6.8. Histidine at 1 mmol/L to 10 mmol/L significantly reduced the percentage of cells that underwent phosphatidylserine translocation and propidium iodide uptake. The effect of the dipeptide buffer, glycylglycine, and the two other positively charged amino acids, arginine and lysine, after 4 hours incubation was compared with histidine at 1 mmol/L. At 1 mmol/L, histidine was superior to arginine and lysine and indistinguishable from glycylglycine. Intracellular free radical production was measured at 0.5 mmol/L, 1.0 mmol/L, and 10 mmol/L histidine concentrations. There was significant inhibition only at 10 mmol/L.

Conclusions: Characteristics of apoptotic cell death that occur in cells suspended in RL are inhibited by the addition of histidine, arginine, and lysine as well as the dipeptide glycylglycine, which, with a pKa of 8.25, also buffers in the physiologic range. Histidine is superior to lysine and arginine at 1 mmol/L. The salutary effect of histidine at 0.5 mmol/L and 1 mmol/L is caused by a mechanism other than the inhibition of oxygen free radicals. Moreover, the buffering of protons may play a role at 24 hours but made no difference at 4 hours.

Key Words: Ringer’s lactate, Histidine, Cell shrinkage, Jurkat cells, Apoptosis, Lymphocytes.


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From the LSU Health Sciences Center, Shreveport, LA.
Address for reprints: Cuthbert Ormond Simpkins, MD, 1501 Kings Highway, Shreveport, LA 71130; email: csimpk@lsuhsc.edu.
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Cell Culture
Jurkat cells were obtained from American Type Culture Collection (ATCC; Manassas, VA). Cells were cultured in RPMI 1640 with NaHCO₃ and without phenol red and L-glutamine (Sigma Aldrich). Each liter of medium contained 10% fetal bovine serum (ATCC), and 10 mL antibiotic-antimycotic solution (Cellgro by Mediatech, Herndon, VA). Incubation of cell culture was performed in an atmosphere of 95% air and 5% carbon dioxide at 37°C. Cells were matured for at least 10 days before they were used in experiments. A concentration of 1 × 10⁶ cells/mL was used in all experiments. Cells were counted in a hemocytometer and separated from their culture medium by centrifugation at 125 g for 5 minutes. After centrifugation and decantation, cells were washed once in the studied solution and again complete decantation was effected. After this second spin, cells were resuspended in the solution to be studied and placed in an incubator. After incubation, the procedure varied according to the experiment being performed.

Cell Shrinkage/Light Scatter
Cell shrinkage was assessed by the analysis of forward light scatter (FSC) and side scatter (SS). FSC consists of light that is detected directly past the cell. This parameter increases with an increase in cell volume. SS is light that is deflected at a 90-degree angle, and increases with increased cell structural complexity. We used a Calibur flow cytometer (Becton Dickinson, San Jose, CA). Flow cytometric settings were FSC = 195 with a gain of 2.0 and SS = 804 with a gain of 2.0, both in the linear mode.

Phosphatidylserine Translocation and PI Uptake
After incubation in study solutions, cells were spun at 125 g for 5 minutes, and then washed once in culture

![Fig. 1](image_url). Flow cytometry of cells incubated for 4 hours in medium (A), RL (B), RL + 1 mmol/L histidine (C), and RL + 10 mmol/L histidine (D). The R1 perimeter is based on the forward and side scatter of cells in medium.
medium. To 0.5 mL of cell suspension (5 × 10^5 cells), 10 μL of media binding reagent and 1.25 μL of Annexin V-fluorescein isothiocyanate were added, and the mixture was incubated 15 minutes at room temperature in the dark. After incubation, the mixture was centrifuged at 125g for 5 minutes at room temperature. The cell pellet was then

Fig. 2. Results of flow cytometry with percent of cells in the R1 perimeter compared with cells in medium. Medium is normalized to 100%. #RL significantly different from medium. *Significantly different from medium. +Significantly different from RL. n.s. = not significantly different from medium.

Fig. 3. Flow cytometry of cells incubated for 24 hours in medium (A), RL (B), RL + 1 mmol/L histidine (C), and RL + 10 mmol/L histidine (D).
gently resuspended in 0.5 mL of cold 1× binding buffer and placed on ice in the dark. Ten microliters of PI was added directly before analysis by flow cytometry.

Cells were analyzed on a FACS Calibur flow cytometer using 488-nm excitation and measuring fluorescence emission at 518 nm (fluorescein isothiocyanate) and 620 nm (PI).

Fig. 4. Results of flow cytometry with percent of cells in the R1 perimeter compared with cells in medium. Medium is normalized to 100%. #RL significantly different from medium. *Significantly different from medium. +Significantly different from RL. n.s. = not significantly different from RL.

Fig. 5. Comparison of cells in R1 after 4 hours and 24 hours incubation in RL + 1 mmol/L histidine and pH 6.8 or 7.4. Solid bars represent cells at pH 6.8 and cross-hatched bars represent cells at pH 7.4. At 4 hours, there was no difference between the two pH values. After 24 hours incubation, fewer cells incubated at pH 6.8 were in R1 than those incubated at pH 7.4. n.s., no significant difference between pH 24 and 6.8 after 4 hours incubation; **significant difference between pH 7.4 and 6.8 after 24 hours incubation.
Free Radical Production

After incubation, cells were removed from the study solution by centrifugation. Then, cells were resuspended in prewarmed phosphate-buffered saline, containing 2 μmol/L of 2′,7′-dichlorofluorescin and incubated at 37°C for 30 minutes. Samples were centrifuged and resuspended in 0.5 mL of prewarmed phosphate-buffered saline. Samples were kept away from light and oxygen free radicals measured on a FACS Calibur flow cytometer using excitation at 495-nm and emission at 520-nm. To create positive controls, oxidation was stimulated with 100 μmol/L tert butyl hydroperoxide (TBH) and cells were incubated for 30 minutes in an incubator.

Statistical Analysis

The cells suspended in medium were the control and to which data were normalized. The result for cells in medium was made 100%. Data were analyzed using a one-way analysis of variance with Tukey’s test or using Student’s t test with a Dunnet’s correction for multiple comparisons to a control group.

Table 1 The Effect of Histidine on Intracellular Oxygen Free Radicals

<table>
<thead>
<tr>
<th>Test Reagent</th>
<th>% of Control Nonapoptotic Cells ± SE</th>
<th>p for Difference From RL</th>
</tr>
</thead>
<tbody>
<tr>
<td>RL alone</td>
<td>17.9 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Histidine</td>
<td>61.2 ± 4.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Glycylglycine</td>
<td>50.7 ± 6.8</td>
<td>0.015</td>
</tr>
<tr>
<td>Arginine</td>
<td>26.1 ± 7.8</td>
<td>NS</td>
</tr>
<tr>
<td>Lysine</td>
<td>46.2 ± 9.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant.

Histidine Inhibits Degradation of Cells

Fig. 6. Flow cytometry of cells stained with Annexin V (phosphatidylserine translocation) and propidium iodide (cell wall disruption). Cells that have not undergone either change are in the left lower quadrant. Cells that underwent phosphatidylserine translocation are in the right lower quadrant. Cells that have taken up propidium iodide are in the left upper quadrant, and cells that have bound to Annexin V and taken up propidium iodide are in the right upper quadrant.
single control. Results are expressed as the mean percentage ± SE for at least three separate experiments. *Values of *p* < 0.05 were considered as statistically significant. Cell shrinkage is not equivalent to cell viability.

**RESULTS**

**Cell Shrinkage**

In figures 1 and 3, the drawn perimeter (R1) encompasses cells that were suspended in media and that had normal light scatter characteristics. In preliminary experiments in medium, we found that the cells within the perimeter had not undergone phosphatidylserine translocation nor had PI entered the cytoplasm. Figure 1 shows the results of cells suspended for 4 hours in various solutions. In RL alone, approximately 40% of the cells had undergone cell shrinkage. Figure 1A shows cells in medium; Figure 1B shows cells suspended in RL alone; and Figure 1C and D shows cells that were suspended in RL with 1 mmol/L and 10 mmol/L histidine, respectively. Figure 2 shows the effect of all of the concentrations tested.

After incubation in RL for 24 hours, nearly 100% of cells suspended in RL had undergone cell shrinkage (Fig. 3B). Figure 3A shows cells suspended in medium; Figure 3B is a sample of cells suspended in RL for 24 hours; and Figure 3C and D shows the effect of adding 10 and 1 mmol/L histidine, respectively. All concentrations of histidine, 7.8 μmol/L to 10 mmol/L, significantly inhibited cell shrinkage in a concentration-dependent manner as shown in Figure 4. The inability of histidine to completely inhibit the change in light scatter when compared with cells in medium could be caused by the difference in osmolarity between medium and the RL-based solutions.

**Cell Shrinkage at pH 6.8 Versus pH 7.4**

The pH of RL was 6.8; therefore, 6.8 was the pH chosen to compare with cells at a pH of 7.4 after 4 hours and 24 hours of incubation (Fig. 5).

**Phosphatidylserine Translocation and PI Uptake**

Histidine, glycylglycine, arginine, and lysine were studied. In Figure 6, the left lower quadrant contains cells that have undergone neither PI uptake nor phosphatidylserine translocation. Figure 6 illustrates the effect of suspending cells in RL alone for 4 hours. In the example shown, most of the cells are seen to be out of the left lower quadrant. The salutary effect of 1 mmol/L and 10 mmol/L histidine is shown in Figure 6C and D, respectively. Figure 6 shows the result of experiments using 1 mmol/L to 10 mmol/L histidine. The result of direct comparison of histidine, glycylglycine, and two other basic amino acids arginine and lysine at 1 mmol/L on the percentage of cells in the left lower quadrant is shown in Table 1.

The effect of histidine on intracellular OFRs was studied (Fig. 7). In our previous work, we found that the suspension
of cells in RL initially led to a burst of intracellular OFRs, followed by the absence of OFR. In this current study, we again observed the burst of OFR when suspended in RL. However, we did not see a significant decrease in OFR in the presence of 0.5 mmol/L and 1 mmol/L histidine.

**DISCUSSION**

Sydney Ringer was a British clinician and physiologist who developed a solution termed Ringer’s solution. He was born in 1835 in Norwich, England, and died in 1910 in Lastingham, Yorkshire, England. The Ringer’s solution did not contain lactate. Sodium lactate was added by Alexis Hartman, an American physician who lived from 1898 to 1964. He had an interest in pediatrics and developed the solution with the intention of treating acidosis in children (Wikipedia http://en.wikipedia.org/wiki/Ringer’s lactate). RL has served the original intention for its creation well. However, we currently administer large amounts of RL for patients with hemorrhagic shock. During hemorrhagic shock, the induction of mediators and cell death occurs. RL and other resuscitation fluids are not designed for this purpose. Yet, of the crystalloid solutions that have been studied, RL is the best that we have in terms of cellular degradation. Craig and Poole compared the survival of rats subjected to uncontrolled hemorrhage and resuscitated with RL to those given no resuscitation. There was no significant difference.

Histidine has been previously shown to be protective of B lymphocyte hybridomas suspended in nutritionally depleted media. Histidine has also been used as a primary component of cold organ preservation solutions. Histidine as a free radical scavenger has been shown to be protective in a rat model of transient forebrain ischemia and in cardiac reperfusion injury. We have confirmed our previous findings that when suspended in RL, cells undergo changes that are consistent with apoptosis, namely cell shrinkage, phosphatidylserine translocation, and disassembly of the plasma membrane, as indicated by the uptake of PI. Our current studies demonstrate that these changes can be greatly reduced by the addition of histidine. In addition, we have shown that glycyglycine also reduces the development of phosphatidylserine translocation and PI uptake. Other basic amino acids, lysine and arginine, also effectively reduced these changes but were not as potent as histidine.

We decided to study histidine based on its ability to buffer protons in the physiologic range. Glycyglycine was chosen for the same reason. However, experiments in which we compared the effect of histidine on cell shrinkage at pH 6.8 and 7.4 showed no difference at 4 hours. After 24 hours incubation, cells that had an initial pH of 6.8 underwent a greater amount of cell shrinkage than cells incubated at an initial pH of 7.4. This suggests that the buffering property of histidine might be important in the long-term, but in the short-term, in the time frame of acute hemorrhage, pH may not be an important factor.

We demonstrated that histidine inhibited intracellular OFR production at 10 mmol/L. But at concentrations that were also effective in enhancing cell survival, 1 mmol/L and 0.5 mmol/L, there was no significant effect on OFR production. Therefore, although the inhibition of OFRs could play a role at higher histidine concentrations, it is unlikely to play a role at lower concentrations. In fact, we cannot assume that the inhibition of OFRs is beneficial.

**CONCLUSIONS**

Histidine significantly reduced the cellular degradation that occurred when cells were suspended in RL. Neither the ability to act as a physiologic buffer nor the inhibition of OFRs explains this protective effect. The other positively charged amino acids, arginine and lysine, and the dipeptide buffer glycyglycine also inhibited phosphatidylserine translocation and plasma membrane disassembly. Histidine was more potent than arginine and lysine and no difference in efficacy between histidine and glycyglycine was demonstrated. The effect of histidine on cell shrinkage was found not to be pH dependent at 4 hours but was pH dependent at 24 hours with an initial pH of 6.8 causing an increased cell shrinkage compared with an initial pH of 7.4. Histidine at a concentration of 10 mmol/L and an incubation period of 4 hours inhibited the production of intracellular OFRs, but there was no effect on free radical production at 0.5 mmol/L or 1 mmol/L. Therefore, the protective effect of histidine at 0.5 mmol/L and 1 mmol/L cannot be caused by OFR inhibition. We do not know the mechanism of these effects. We found that cell shrinkage was inhibited at concentrations as low as 7.8 μmol/L. In this concentration range, it is unlikely that histidine is effective as a buffer or as a free radical scavenger. Moreover, histidine has an imidazole side chain but glycyglycine does not have a side chain at all, yet both are effective. It is possible that histidine acts at a cellular binding site that has not yet been identified and that may be common to other amino acids. In future experiments, we will explore this possibility.

**ACKNOWLEDGMENTS**

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Thresholded Area Over the Curve of Spectrometric Tissue Oxygen Saturation as an Indicator of Volume Resuscitability in Porcine Hemorrhagic Shock

Sven Zenker, MD, Patricio M. Polanco, MD, Hyung Kook Kim, MD, Andres Torres, MD, Yoram Vodovotz, PhD, Gilles Clermont, MD, Michael R. Pinsky, MD, Donald A. Severyn, MS, and Juan Carlos Puyana, MD

**Background:** A rapid, reliable, and noninvasive functional measure of responsiveness to resuscitation in posttraumatic hemorrhagic shock could prove useful in guiding therapy, especially under circumstances such as the battlefield and civilian mass casualties. Tissue oxygen saturation (StO2) is a promising candidate for this application. We therefore explored the value of peripheral muscle StO2 in predicting systemic responsiveness to colloid volume resuscitation in a porcine model of hemorrhagic shock.

**Methods:** Fourteen isoflurane-anesthetized piglets were subjected to a standardized hemorrhage protocol that maintained mean arterial pressure (MAP) between 30 and 40 mm Hg. Asanguineous resuscitation with a volume of Hextend equal to the total volume bled was initiated when compensation was exhausted (MAP < 30 mm Hg). We recorded continuous MAP and StO2 values, and calculated the contiguous area over the StO2 curve yet below a given threshold of StO2 (TAOC) as a function of this threshold before the selected timepoint for timepoints up to 30 minutes before resuscitation.

**Results:** Hemorrhage resulted in significant fluctuations of MAP and high interindividual variability of disease dynamics and outcome: 4 nonsurvivors and 10 survivors at 2 hours postresuscitation. StO2 measurements reflected hemodynamic conditions in most animals, with a pronounced drop preceding final decompensation in 7 of 14 animals. TAOC discriminated three of four nonresuscitable (nonsurvivor) animals from the survivors, with group differences reaching significance even for the earliest examined timepoint (30 minutes before resuscitation), depending on the choice of TAOC threshold.

**Conclusions:** StO2 may serve as a marker of decompensation, whereas TAOC, a physiologically motivated correlate of perfusion debt and cumulative hypoperfusion injury, may be a useful early indicator of responsiveness to volume resuscitation in hemorrhagic shock.

**Key Words:** Hemorrhagic shock, Irreversibility, Reversibility, Volume resuscitation, Tissue oxygen saturation, Oxygen deficit, Noninvasive measurement.

DOI: 10.1097/TA.0b013e3181f6095

Understanding the transition from reversible to irreversible hemorrhagic shock has been the subject of numerous studies during the past decades.1–6 A meaningful definition of irreversibility inherently needs to make explicit the therapeutic interventions under which the shock state fails to improve, such as volume resuscitation or pressor therapy.

A definition particularly relevant for the prehospital and battlefield settings is that of reversibility with volume resuscitation (volume resuscitability, VR). Therapeutic interventions in these settings are limited (typically to local control of hemorrhage and volume resuscitation). Yet, the demand for resuscitation fluid in a civilian mass casualty or battlefield setting may exceed available supply. Furthermore, it is desirable to optimize volume resuscitation to avoid exacerbating bleeding from uncontrolled hemorrhage sites. Diagnostic tools that could accurately predict a patient’s responsiveness to volume resuscitation would enable adjusting volume therapy to the minimum necessary to ensure resuscitability once bleeding is controlled and optimize allocation of a limited resource without negatively impacting outcome.

The near-infrared spectrometric measurement of tissue oxygen saturation (StO2) in peripheral muscle is a technology that is both noninvasive and easily portable. Making use of the oxygenation-dependent differential absorption characteristics of hemoglobin and, to a much lesser degree, myoglobin, this measure quantifies the oxyhemoglobin fraction, or percentage of oxygenated hemoglobin in the observed muscle.7,8 Previous studies have shown that StO2 correlates well with invasively measured mixed venous oxygen saturation and severity of hemorrhagic shock, and tracks systemic oxygen...
delivery in trauma patients. The dynamic changes in StO2 under cuff inflation-induced forelimb ischemia may quantify cardiovascular reserve and correlate with clinical indices of severity in sepsis in a critical care setting, whereas the StO2 values after a first resuscitation step predict outcome in an experimental model of hemorrhagic shock. Recent results indicate that StO2 debt may be predictive of later development of multiple organ dysfunction in trauma victims. However, StO2 measurements alone before any resuscitation or other intervention have not been shown to be predictive of VR, although this would be desirable in nonhospital emergency settings.

Motivated by the preliminary indications of the possible threshold characteristics of the StO2 relationship to outcome and careful physiologic considerations, we developed the thresholded area over the curve (TAOC) as a new index derived directly from continuous StO2 measurements and evaluated its ability to predict VR in a severe porcine model of hemorrhagic shock and volume resuscitation.

**MATERIALS AND METHODS**

**Experimental Protocol**

The University of Pittsburgh Institutional Animal Care and Use Committee approved the study. Animal care and handling conformed to National Institute of Health guidelines. The experimental hemorrhage protocol was designed to simulate a dynamically changing clinical situation reproduced by modifying a Wiggers model using progressive, discrete bleeding episodes based on the animal’s physiologic response. Lightly anesthetized (isoflurane 1%–2% inspiratory concentration) and mechanically ventilated female Yorkshire/Durock pigs of approximately 25 kg were instrumented with standard hemodynamic monitoring equipment including electrocardiogram (EKG) signals and invasive blood pressure measurements. StO2 values were recorded continuously using the InSpectra tissue spectrometer (Hutchinson Technology, Hutchinson, MN).

The following arterial pressure-driven experimental hemorrhage protocol was performed to exhaust the animals’ compensatory capacity progressively with respect to hemorrhage and thus approach the individual boundary of irresponsibility: (1) assess baseline physiology 15 to 30 minutes after instrumentation; (2) bleed at a rate of 60 mL/min to a mean arterial pressure (MAP) of 30 mm Hg; (3) sustain this state for a maximum of 90 minutes after last bleed if MAP is spontaneously maintained between 30 and 40 mm Hg, or return to step 2 by reinitialization of bleeding if the animal is capable of compensating to a MAP of ≥40 mm Hg, yet proceed to step 4 if MAP goes below 30 mm Hg for ≥15 minutes after the end of the previous bleeding; (4) resuscitate animal with Hextend (Hospira Inc, Lake Forest, IL) colloid using the same volume as total volume bled; (5) observe until death or for a maximum of 2 hours after step 4.

**Data Acquisition**

Hemodynamic data were recorded using the Ponemah P3Plus and LabView software systems (Data Sciences International, Valley View, OH, and National Instruments Corporation, Austin, TX, respectively). StO2 tracings were recorded using a software package provided by Hutchinson Technologies. All data were subsequently exported to the MATLAB (The MathWorks, Natick, MA) programming environment for visualization and processing.

**Data Analysis and Statistics**

All data are reported as mean ± SD except when otherwise noted. Group comparisons were performed using the nonparametric Wilcoxon rank sum test. Reported p values are two-sided. Two significant digits are reported for StO2 values. Using customized software, we calculated the TAOC of StO2 at the exact timepoint of resuscitation as well as at 1, 2, 5, 10, 15, 20, and 30 minutes before resuscitation for the entire range of feasible threshold values. Earlier timepoints were not examined to avoid biasing the comparison by including early, or even preshock, data as a result of the significant interanimal variability of shock duration. Specifically, the TAOC was calculated by numerical integration of the area between the given threshold and the StO2 curve from the chosen timepoint backwards until StO2 reaches the given threshold (Fig. 1). The physiologically motivated hypothesis underlying this analysis is that both the distance and the duration of StO2 below a given threshold impact cumulative oxygen debt, thus determining resuscitability. The predictive ability of this index was analyzed by comparing TAOC values for survivor and nonsurvivor groups using the nonparametric Wilcoxon rank sum test at the various presuscitation timepoints. The discriminating ability of the resulting tests was quantified by calculating the receiver operating characteristic (ROC) area under the curve (AUC). For comparison purposes, heart rate (HR), mean arterial blood pressure (MAP), and the absolute value of StO2 were subjected to identical analyses. Data processing and analyses were performed using the Matlab 7 package (The MathWorks, Natick, MA) and the SPSS 14 statistics package (SPSS, Chicago, IL).
RESULTS
Hemorrhagic Shock Model

The experimental protocol resulted in significant fluctuations in MAP (Fig. 2). The individual response patterns showed considerable variability among animals, both in speed and number of recoveries after bleeds: the number of bleeding episodes was 3.6 ± 1.2, volume bled was 52% ± 9.5% of estimated total blood volume, duration of shock until resuscitation was 99 ± 45 minutes. Survivors and nonsurvivors did not differ significantly in any of these variables (data not shown). Ten pigs were alive at the end of the 2-hour postresuscitation observation period, whereas four had died.

StO₂: Absolute Values and Dynamic Behavior

Baseline values of StO₂ were 79% ± 10% and did not differ significantly between survivors and nonsurvivors (80% ± 9% vs. 74% ± 11%, p = 0.23). A typical complete tracing of hemodynamic variables and StO₂ for a resuscitable/survivor animal is shown in Figure 2. A pronounced drop in StO₂ clearly preceding hemodynamic decompensation (inability to maintain MAP above 30 mm Hg) was observed in 7 of the 14 animals. Absolute values of StO₂ at the timepoint of resuscitation were 58% ± 18%. Survivors had higher absolute StO₂ values at the timepoint of resuscitation (64% ± 16% vs. 43% ± 12%, p = 0.048).

TAOC

The TAOC of StO₂ was calculated for all integer thresholds between 40% and 100% of baseline. Three of the four nonresuscitable animals were clearly separated from the survivor group for a wide range of thresholds for all timepoints for which the group comparisons were performed. The single nonresuscitable animal that could not be discriminated differed from the other nonresuscitable animals in that it succumbed to ventricular fibrillation before completion of the resuscitation protocol. Figure 3 depicts the threshold dependency of the TAOC index for all animals at the timepoint 30 minutes before resuscitation, where it can be observed that statistical significance is reached for a choice of threshold between 67% and 75%. Furthermore, it was observed that the range of statistical significance tended to move toward lower threshold values for timepoints closer to resuscitation (data not shown).

Comparison of Discriminatory Abilities

*p* values of the Wilcoxon rank sum test comparing the survivor with nonsurvivor groups are shown in Figure 4 for all examined timepoints for the MAP, HR, StO₂, and TAOC calculated for a 75% threshold. This figure shows that although MAP is the best discriminator of survival at the timepoint of resuscitation, this measurement loses all discriminatory ability for timepoints earlier than 120 seconds before resuscitation. A similar observation can be made for heart rate. Absolute values of StO₂ are comparable in discriminatory ability to TAOC at the timepoint of resuscitation, whereas TAOC is superior to all other indices for timepoints earlier than 600 seconds before resuscitation. Similar observations can be made if other reasonable thresholds for TAOC are chosen. However, the time at which discrimination is best will depend on this choice, with a trend toward better early discrimination at higher thresholds (data not shown). Figure 5 allows comparison of ROC for MAP, HR, StO₂, and TAOC for a threshold of 75% for the timepoint 30 minutes before resuscitation. It is evident that TAOC with a ROC AUC of 0.838 still provides useful discrimination between survivors and nonsurvivors 30 minutes before resuscitation. In contrast, MAP and HR have ROC AUCs of 0.35 and 0.4, respectively.
DISCUSSION

Hemorrhagic Shock Model

The experimental protocol described herein provides a model of severe hemorrhagic shock that allows for a wide range of hemodynamic fluctuations in the course of the experiment, reflecting the animals’ compensatory responses. Consequently, the model was associated with significant interanimal variability in time courses and outcome. We suggest that these characteristics make this experimental paradigm particularly suitable for the practical assessment of dynamic response characteristics of noninvasive monitoring equipment.

Fig. 3. Characteristics of the TAOC index as a function of selected threshold 30 minutes before resuscitation. Three of the four nonsurvivors are clearly separated from the survivors over a wide range of thresholds. The top panel displays the thresholded area over the curve (TAOC) of StO2 30 minutes before the resuscitation as a function of the applied threshold for nonresuscitable/nonsurvivor animals (dashed lines) and resuscitable/survivor animals (solid lines). The bottom panel shows p values for group comparison of the TAOC for resuscitable versus nonresuscitable animals as a function of the threshold.

Fig. 4. Predictive ability of volume resuscitability of various physiologic indices. Depicted are Wilcoxon rank sum test p values for comparison between survivors and nonsurvivors for mean arterial pressure (MAP), heart rate (HR), StO2, and TAOC of StO2 for a threshold of 75% for various timepoints before the timepoint of resuscitation. The timepoint of resuscitation is represented to the very right of the graph, whereas timepoints further to the left correspond to earlier timepoints up to 1,800 seconds (30 minutes) before resuscitation.
In agreement with previous studies, $StO_2$ usefully tracked the progression of shock severity in most animals. It clearly anticipated the final decompensation in only 50% of the animals. Its absolute values at the timepoint of resuscitation differed between resuscitable and nonresuscitable animals, with discriminatory ability declining for earlier timepoints.

The TAOC clearly discriminated three of the four nonresuscitable animals from the resuscitable ones over a wide range of thresholds (Fig. 3) and for timepoints as early as 30 minutes before decompensation and subsequent resuscitation (Fig. 4). This finding points to the possibility of developing threshold values that might prove useful for decision-making purposes. The one animal whose outcome could not be predicted using this index died of ventricular fibrillation before complete resuscitation, which may explain this failure. The TAOC is essentially a measure of peripheral perfusion debt, whereas the sudden onset of arrhythmia might point to a primarily cardiac rather than peripheral cause of circulatory failure in that animal. Although this observation may be interpreted to further support the usefulness of the TAOC, exclusion of this animal from the analysis on these grounds alone did not seem legitimate because the experimental protocol did not provide for such an occurrence a priori.

The range of timepoints at which nonparametric statistical group comparison for difference of medians reached significance depended on the choice of threshold. Higher thresholds tended to yield significant differences for earlier timepoints, whereas lower threshold values appeared more valid for later timepoints (i.e., timepoints closer to the timepoint of resuscitation). The threshold range at which we identified statistically significant differences between survivors and nonsurvivors almost exactly coincides with the 75% threshold proposed in previous studies as a predictor of the development of multiple organ dysfunction. ROC analysis indicated that the TAOC may actually provide a useful discriminatory test and may be superior to traditional indices such as HR or MAP (Fig. 5). The TAOC also appears to discriminate outcome better than the instantaneous $StO_2$ values upon which its calculation is based.

Subject to further validation, this study points to the potential usefulness of $StO_2$ TAOC as an indicator of volume resuscitability with potentially higher and thus more practically useful discriminatory power than the single $StO_2$ reading. Because it takes both absolute value and duration into account, this index might eventually serve to

![Fig. 5. Receiver operating characteristics (ROC) and areas under the curves (AUC) for discrimination of survivors and nonsurvivors. ROC AUC were calculated 30 minutes before the timepoint of resuscitation for mean arterial pressure (MAP), heart rate (HR), $StO_2$, and TAOC of $StO_2$ for a threshold of 75%. Diagonal segments are produced by ties.](image-url)
estimate sustainable shock times before resuscitation is bound to fail in the individual patient. This noninvasive index may thus yield a powerful tool for resource allocation under strenuous condition or in cases in which resuscitative interventions cannot be provided immediately (such as in mass casualty settings and irregular warfare scenarios). Larger studies are required to validate the utility of \( \text{StO}_2 \) TAOC as an accurate predictor of the ability to resuscitate posttraumatic hemorrhagic shock.

Concerning the practicality of using this index in a prehospital scenario, it should be noted that calculation of the TAOC could easily be implemented in the already computerized measurement device, relieving the user of all computational difficulties.

**Limitations of the Study**

A limitation of this controlled experimental setup lies in the fact that the animals are ventilated and anesthetized. This aspect of our experiments may limit the applicability of the results presented herein to real-life scenarios, because the physiologic compensation mechanisms that play an important role in the acute phase of trauma are altered by anesthesia. We note that the level of anesthesia administered after initiation of shock was minimized to the lowest acceptable levels according to federal and institutional animal care regulations. We therefore suggest that tissue oxygenation measurements should be more robust than other noninvasive measures, e.g., sublingual CO\(_2\) partial pressure measurements, which may be severely altered by the typical hyperventilatory response of spontaneously breathing trauma victims. Furthermore, the applicability of our results is naturally limited to the specific resuscitation protocol used. Our ability to explore the earliest time point at which the TAOC can discriminate later VR in this model was limited by the relatively short duration of shock in the animals, and this issue warrants further study.

**CONCLUSIONS**

\( \text{StO}_2 \) reliably tracks severity of hemorrhagic shock, whereas the TAOC, a physiologically motivated correlate of perfusion debt and cumulative hypoperfusion injury, may be a useful early indicator of responsiveness to volume resuscitation in hemorrhagic shock. This index may eventually allow for the prediction of sustainable time in a given shock state after which volume resuscitation will still be effective.

**ACKNOWLEDGMENTS**

We acknowledge the invaluable assistance of Lisa Gordon in performing this study.

**REFERENCES**


**DISCUSSION**

Dr. Henry Schiller (Rochester, Minnesota): Near-infrared spectroscopy is an appealing idea to monitor the trauma patient, because it is noninvasive and presumably it helps you determine oxygen delivery based on tissue oxygenation, based on the spectrometric scatter or reflectance of oxyhemoglobin and deoxyhemoglobin.

The Achilles heel, however, of any of the noninvasive techniques is that they depend on a number of assumptions made in biologic systems that may or may not be held up in the real-world clinical situation.

In the case of near infrared spectroscopy, assumptions need to be made regarding optical scatter and optical path length, which leads to a lot of interference from things, such as adiposity, pigmentation, and so on and so forth.

There’s been reported a wide variation in values even in normal subjects and significant differences in males versus females, different ethnic groups, smokers versus nonsmokers, and it’s been shown to correlate with increasing age and increasing body mass index.
Moreover, hemoglobin and myoglobin share the same absorbance wavelengths and so although it’s generally believed that what you’re measuring is hemoglobin, in a hemorrhagic shock model where you’re looking at muscle, myoglobin may become a more significant contributor to the signal that you’re getting.

The problem with this is that there is a lot of variability between individuals, which really limits your ability to determine an absolute value for this and so the authors are to be commended for looking at dynamic changes to try to overcome this problem.

The other thing to remember is that there have been conflicting results reported in the literature, particularly in the report by McKinley et al., which looked at both subcutaneous StO2 and muscle StO2 and found that although muscle seemed to have shunted the blood away, StO2 and subcutaneous tissues remained very good, which sort of goes against the path of physiology or shock that we understand.

Understanding these pitfalls, again, I would like to commend the authors on their efforts to define the usefulness of this technique. I have just a few questions.

For the threshold area under the curve, it looks like the threshold of what you’re actually reporting is a percentage of baseline StO2 that you measured at the beginning of the study. That’s fine for a laboratory situation and that’s fine for well-defined periods of shock like you may have with cardiopulmonary bypass, for example, but is it really useful for the trauma patient for whom you don’t really have this baseline data to generate your threshold? If you don’t have a baseline, can you still figure out some way of doing a threshold under the curve?

The next question is in regard to generating the threshold over the curve. Is this something that you can really do at bedside clinically or is this going to require a retrospective review kind of after the fact?

Finally, when comparing threshold values of StO2 with threshold values of minimal systolic blood pressure, it turns out that minimal systolic blood pressure has been shown by McKinley et al. to be more sensitive than StO2. Did you look at that? Did you compare the InSpectra device to simple noninvasive blood pressure measurements?

Dr. Sven Zenker (Pittsburgh, Pennsylvania): Let me first of all address your first question and there, I have to sort of excuse myself for probably not making this issue clearer, and I realize that this is a fairly complicated setting that we’re talking about here.

In actual fact, we do use the absolute values of StO2. There is no usage of baseline StO2 at all in this particular calculation and so, in fact, we would not need to know a baseline StO2 or make an assumption about population values at all to be able to calculate this.

This brings me directly to your second question, is this doable in a clinical or bedside setting? I would contend that yes, it is, given that we measure continuously for at least some period of time. The calculation itself is really trivial. It amounts to numerical integration and subtraction.

The devices used today are fully computerized and the algorithm used is trivial. It’s basically a couple of lines of Matlab. I would think that implementing this into a real-life device would be relatively trivial and a good point about it is that it would not incur any additional costs at all, because it’s just a software thing, basically.

Dr. John T. Malcynski (Lancaster, Pennsylvania): I have two questions. Number one, it seems like the graph on your unresuscitated porcine model showed that the mean arterial pressure actually was responsive prior to the StO2, which means that if we were to base a resuscitation on the StO2 that it would be delayed. Maybe you can explain to me how that would be beneficial, because if you started your resuscitation earlier, you probably wouldn’t see a drop in StO2 after that.

My second question is, I’m not sure that I understand the practicality of how this would be used in particular a mass casualty situation, which was part of your hypothesis, because it seems to be quite involved and equipment intensive. Maybe you can just comment on that.

Dr. Sven Zenker: Let me briefly answer Dr. Schiller’s question first, which was how does this relate to mean arterial pressure, and, in fact, we’ve done the exact same analysis for mean arterial pressure and in this particular experimental setup, where the mean arterial pressure is actually within a fairly narrow range, since we use it as a decision criterion to actually initialize the resuscitation and it doesn’t have much discriminatory power as to StO2.

This particular model is clearly better and to come to your question, does it respond earlier, I would contend that our model is not really that useful to answer this particular question, because, as I said, our experimental decisions are based on mean arterial pressure alone and so we do not have any large or large enough variability between animals to actually analyze for this particular question.

Although we cannot, from the current data, really state this, I’m fairly hopeful that it should be possible to actually detect with a certain safety margin a time where resuscitation is still possible, even when mean arterial pressure was above 30 mm Hg during the shock phase of the experiment, except at the time of resuscitation, and so we should be able, hopefully, to detect earlier than we could based on mean arterial pressure alone.

Again, this is sort of limited in its applicability to the real-life setting, because we are controlling, in a sense, arterial blood pressure here. I’m not really confident to make any statement with regard to that, based on our data, but it does seem like it might be promising.

The applicability in a mass casualty setting is a good point, because, as I said, the additional information we are able to integrate and thus, improve our results, relies on having sequential measurements over a certain amount of time.
For quick decision making, like within 30 seconds after seeing the patient, this is not a useful method. As I’ve heard from colleagues who work, for example, in the military scenarios, it does seem to be a problem to take care of the patients in the in-between phase between initial injury and full hospitalization and this seemed to be because resources are limited, for example, during transport.

This might prove applicable, from what I can see, to actually during this intermediate phase to detect which patients need immediate care and which patients can actually go up for later treatment in the hospital setting. That would be one potential application that I could see.

I fully agree that if the triage decision is to be made within 30 seconds that this does not add anything to the single measurement.
Acute Effects of TASER X26 Discharges in a Swine Model

Andrew J. Dennis, DO, Daniel J. Valentino, MD, Robert J. Walter, PhD, Kimberly K. Nagy, MD, Jerry Winners, BS, Faran Bokhari, MD, Dorion E. Wiley, MD, Kimberly T. Joseph, MD, and Roxanne R. Roberts, MD

Background: Very little objective laboratory data are available describing the physiologic effects of stun guns or electromuscular incapacitation devices (EIDs). Unfortunately, there have been several hundred in-custody deaths, which have been temporally associated with the deployment of these devices. Most of the deaths have been attributed to specific cardiac and metabolic effects. We hypothesized that prolonged EID exposure in a model animal system would induce clinically significant metabolic acidosis and cardiovascular disturbances.

Methods: Using an Institutional Animal Care and Use Committee-approved protocol, 11 standard pigs (6 experimental and 5 sham controls) were anesthetized with ketamine and xylazine. The experimental pigs were exposed to two 40-second discharges from an EID (TASER X26, TASER Intl., Scottsdale, AZ) across the torso. Electrocardiograms, blood pressure, troponin I, blood gases, and electrolyte levels were obtained pre-exposure and at 5, 15, 30, and 60 minutes and 24, 48, and 72 hours post-discharge. p values <0.05 were considered significant.

Results: Two deaths were observed immediately after TASER exposure from acute onset ventricular fibrillation (VF). In surviving animals, heart rate was significantly increased and significant hypotension was noted. Acid-base status was dramatically affected by the TASER discharge at the 5-minute time point and throughout the 60-minute monitoring period. Five minutes postdischarge, central venous blood pH (6.86 ± 0.07) decreased from baseline (7.45 ± 0.02; p = 0.0004). Pco2 (94.5 mm Hg ± 14.8 mm Hg) was significantly increased from baseline (45.3 mm Hg ± 2.6 mm Hg) and bicarbonate levels significantly decreased (15.7 mmol/L ± 1.04 mmol/L) from baseline (30.4 mmol/L ± 0.7 mmol/L). A large, significant increase in lactate occurred postdischarge (22.1 mmol/L ± 1.5 mmol/L) from baseline (1.5 mmol/L ± 0.3 mmol/L). All values returned to normal by 24 hours postdischarge in surviving animals. A minor, nonsignificant increase in troponin I was seen at 24 hours postdischarge (0.052 ng/mL ± 0.030 ng/mL, mean ± SEM).

Conclusions: Immediately after the discharge, two deaths occurred because of ventricular fibrillation. In this model of prolonged EID exposure, clinically significant acid-base and cardiovascular disturbances were clearly seen. The severe metabolic and respiratory acidosis seen here suggests the involvement of a primary cardiovascular mechanism.

Key Words: Taser, Electromuscular incapacitation, Acidosis, Electrocardiograph.

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Supported solely by departmental research funds derived from the Cook County Trauma Unit.
Address for reprints: Robert J. Walter, PhD, Department of Trauma, Rm 1300, Stroger Hospital of Cook County, 1900 West Polk St., Chicago, IL 60612; email: rwalter@cookcountytrauma.org.
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ment about what load is appropriate or representative, (3) the lack of a standard model for study in vitro or in vivo, and (4) a general disinclination for academic scientists to study these devices because they are viewed as weapons.3-5,7 Under no-load conditions, the TASER X26 delivers DC pulses at a voltage of about 50 kV, with a pulse duration of 140 μs, a frequency of 19 Hz, and power of 0.36 J/pulse (www.taser.com). In vivo, this type of discharge causes severe pain, strong muscle contractions, and incapacitation of volitional movement. However, Ruggieri7 asserts that the peak currents achieved by the TASER under physiologic resistive loads can be many times higher than 2.1 mA and may easily exceed the ventricular fibrillation (VF) threshold. As a result of such disparities, the safety profile and effects of EID current exposure on the function and structure of living tissue cannot be extrapolated reliably.

Many of the initial studies on EIDs were performed on the much less powerful first or second generation devices.8-10 The recent peer-reviewed literature on fourth generation EIDs (such as the TASER X26) is still emerging and the results are conflicting. Some studies, using a TASER-like device, showed no evidence of acute dysrhythmia and a large safety margin for the development of ventricular dysrhythmia in swine.4,11 Similarly, neither acidosis nor hyperkalemia have been observed in healthy human volunteers exposed to brief (2.7 seconds on average) TASER X26 discharges.12,13 However, in swine models, Jauchem et al.14 showed the development of significant acidosis, and Webster et al.15 and Nanthakumar et al.16 have shown the potential for fatal dysrhythmias with TASER X26 exposure. Such conflicting results make it difficult to establish guidelines regarding the need for treatment or even monitoring of the increasing number of patients who arrive in emergency rooms after exposure to EID discharges.

In an attempt to reconcile some of the conflicting information about the effects of TASER discharges, we have studied the effects in a well-characterized swine model. Our working hypothesis was that subcutaneous discharges from the TASER X26 can produce significant cardiac effects including acute dysrhythmia or VF and that these effects may be exacerbated by concomitant acidosis or electrolyte and biochemical abnormalities.

**MATERIALS AND METHODS**

**Animals and Groups**

Three- to 6-month-old Yorkshire pigs (Michael Fanning Farms, Howe, IN) weighing between 22 kg and 46 kg were used. The experimental group (80-second thoracic discharge) and the negative or sham control group, were comprised of six and five animals, respectively. The size of the animals used in our study correlates with that of children, teenagers, and some adult humans with small frames. Other investigations of TASERS have used animals in a similar size range.4,11,14,16 The Institutional Animal Care and Use Committee (IACUC) for the Hektoen Institute for Medical Research, LLC reviewed and approved this project.

All animals were deeply anesthetized during each monitoring session using intramuscular and intravenous ketamine (Ketaset; Fort Dodge Animal Health, Fort Dodge, IA) and xylazine (Anased; Lloyd, Shenandoah, IA), and respiratory secretions were inhibited using glycopyrrolate (Robinul; Fort Dodge Animal Health, Fort Dodge, IA). Ketamine/xylazine/glycopyrrolate (30/3/0.01 mg/kg) was administered intramuscularly for sedation and then ketamine and xylazine (5.6/0.8 mg/mL) in sterile saline were instilled intravenously using an infusion pump (Flogard 6200; Travenol, Deerfield, IL) through a 23-gauge cannula placed into an ear vein at a rate of 3 mL·h⁻¹·kg⁻¹ (16.8/2.4 mg/kg). Animals were intubated using cuffed endotracheal tubes (5.0–6.5 mm, Rusch; Kernen, Germany) after anesthetizing the larynx with 0.25 mg/mL to 1.0 mL of sprayed 20% benzocaine (Hurricaine; Beutlich Pharm., Waukegan, IL). Breathing was controlled (15 breaths per minute; tidal volume = 10 mL/kg; minute volume = 150 mL/kg). The TASER X26 was discharged (see below) in two separate 40-second intervals for a total of 80 seconds, during which time the ventilator was shut off but spontaneous breaths were permitted. Two ventilated breaths (within 10 seconds) were administered between the 40-second discharges. Breathing rate was adjusted after discharge according to demand. The purpose of this was to ensure that the ventilator was not the cause of any observed respiratory acidosis. Animals were maintained in dorsal recumbence for all electrical discharges and monitoring procedures. At the conclusion of each monitoring session, intravenous yohimbine (0.05–0.15 mg/kg; Yobine; BenVenue Labs, Bedford, OH) was used to reverse the effects of xylazine and to speed recovery from anesthesia.

Instead of using inhaled halothane or isoflurane anesthesia, ketamine/xylazine was used throughout this study (except for thoracotomized animals). The primary local electrical injury anticipated with these waveforms was membrane electrroporation, particularly of nerve and muscle.17,18 This effect is sensitive to the presence of lipids or highly lipid-soluble agents such as isoflurane, halothane, or barbiturates. The ketamine and xylazine combination used here has also been shown to be an effective general anesthetic in swine19,20 and our data confirm this (see below).

**Test Device**

An unmodified, police-issue TASER X26 device was used to produce electromuscular incapacitation. Because it is illegal for civilians to possess the TASER X26 in Illinois, a member of the local law enforcement community trained in TASER use delivered the discharges. TASER lithium 6 V Digital Power Magazines (DPM) were used as the power source for all discharges. DPM charge state was monitored before and after each discharge and at no time was a DPM used with a charge state less than 70%.

**Experimental Set-Up and EID Discharge**

While in dorsal recumbence, all four limbs of the animal were restrained to the table. The TASER cartridge was fired...
into a towel and the darts were disentangled from the cloth without disrupting any of the fine wires, insulation, or connections. The barbed darts were placed along a line parallel to the cardiac axis. The superior or noncurrent-emitting dart was placed 13 cm superior to the xiphoid process and 5 cm to the right of the midsternal line. The lower or current emitting dart was placed 7 cm to the left of the umbilicus. This dart configuration produced a diagonal separation of approximately 30 cm in each animal and is similar to that used by Jauchem et al.\textsuperscript{14} For two of the six animals in the experimental group, the superior dart was the current emitting dart. All darts were manually inserted perpendicular to the skin and to the maximum depth allowed by the length of the barbed end (3/8 of an inch) such that the dart tip was located in subcutaneous tissue. For TASERs discharged from distances less than 11 feet, skin penetration has been shown to occur for both darts in approximately 65% of TASER strikes in the field.\textsuperscript{21}

The TASER X26 was discharged in two separate 40-second intervals for a total of 80 seconds, during which time the ventilator was shut off but spontaneous breaths were permitted. Two ventilated breaths were administered during the 10-second pause between the 40-second discharges. The discharge times of stun devices as used in the field vary greatly. Often short bursts (\textasciitilde5 seconds) are sufficient to subdue most subjects, but the devices are capable of delivering very prolonged, continuous discharges. The only practical limit on the discharge duration is the amount of battery power available, so continuous discharges could be administered for more than 10 minutes and instances of discharges longer than 90 seconds have been reported for TASERs.\textsuperscript{22} Subjects are usually incapacitated almost immediately upon exposure to TASER discharges but they regain muscle control very rapidly after discontinuation of the discharge. Highly combative subjects may receive prolonged or repeated discharges, during which time officers can approach and restrain them.

### Cardiac Rhythm and Echocardiography

Cardiac rhythm was evaluated and monitored continuously during anesthesia using a five-lead electrocardiogram (EKG) and monitor (Datex instruments, Helsinki, Finland) and at each experimental time point 10- to 15-second tracings were printed and retained. EKGs were also recorded throughout the duration of the discharge. Because of the amount of electrical interference created by the TASER discharge, EKGs done during the discharge were unreadable. To adequately assess the rhythm and function of the myocardium, echocardiography was performed using a Sonosite 180 with a 2-MHz probe (Sonosite Inc. Bothell, WA) on four of the six experimental animals. Echo images were first obtained predischarge to establish a baseline for each animal in the left parasternal axis. Echocardiography was then continued during and after the TASER discharge to assess, in real time, any changes that occurred in myocardial rhythm and function. Video records of each echo were digitally recorded for further analysis.

### Controls

Five sham control animals were studied for 72 hours using the same paradigm as that used for animals exposed to TASER discharges except that they were not exposed to any discharges during the monitoring period. At the completion of the 72-hour blood sampling and monitoring period, two of these sham animals underwent thoracotomy. Each of these animals then received two 40-second TASER discharges while direct visual monitoring was performed. Each of these animals was physiologically normal before these discharges according to all blood chemistries, vital signs, and EKG. These animals had received no previous TASER discharges. In addition, baseline intra-animal data were obtained for all 11 (6 experimental and 5 sham controls) animals studied.

### Thoracotomy

To further document cardiac activity, two 40-second discharges were administered to two of the five control animals (31 kg and 46 kg) just before being euthanized (see above). Left anterior thoracotomies were performed under inhaled anesthesia with 1.5% to 2% isoflurane. Electrocautery was avoided to eliminate any non-EID electrical exposure. An incision approximately 10-cm long was made over the left anterior thorax in the fifth or sixth intercostal space. Sharp dissection was carried down to access the left thorax. A rib spreader was used to expose the heart and lungs. The rib spreader was placed outside the current path between the darts and it was not in direct contact with the heart. The left lung was retracted out of the field with gauze sponges. The pericardium was opened sharply facilitating a direct view of the beating myocardium. The TASER darts were then placed in the manner previously described and two 40-second discharges were administered. The 31-kg animal received the second 40-second discharge with the superior dart as the current emitting dart. Cardiac activity was directly monitored and recorded before, during, and after TASER discharge for subsequent analysis and comparison with echocardiographic data.

### Blood Samples and Analysis

There were eight time points at which central venous blood was drawn from the precaval venous complex, and vital signs (tissue oxygen saturation, heart rate, and blood pressure [BP]), and additional EKGs were recorded. The sampling time points included predischarge (time 0) and 5, 10, 15, 30, 60 minutes, 24, 48, and 72 hours postdischarge. Animals were euthanized according to American Veterinary Medicine Association standards after the 72-hour time point by switching the anesthesia to 5% inhaled isoflurane and injecting 3 mol/L KCl into the heart.

Immediately after being drawn, each blood sample was placed into heparinized and plain vacutainer tubes. The heparinized blood was tested using an iSTAT analyzer (Abbott Point-of-Care, Abbott Park, IL) using CG8+, CG4+, creatinine, and troponin I (TnI) cartridges. These cartridges return
data on pH, Pco₂, bicarbonate, lactate, potassium, TnI, and creatinine. Blood samples were stored on ice for a maximum of 2 hours, centrifuged (3,000g for 15 minutes at 4°C), plasma and serum aliquoted into 400 µL microcentrifuge tubes, and samples stored at -85°C until use. Serum from each time point was thawed and assayed for creatine kinase-MB isoform (CK-MB) and myoglobin using microplate enzyme-linked immunosorbent assays.

When whole blood lactate values exceeded the CG4+ maximum value of 20.0 mmol/L, the aliquoted serum was diluted 1:1 with normal saline (0.9% NaCl). The diluted serum was then assayed using a CG4+ cartridge to get a numerical lactate value. This value was then doubled and entered into the data set. This dilution method was validated by first diluting iSTAT standards in a similar fashion and analyzing them using a CG4+ cartridge. The values obtained for the diluted iSTAT standards were one-half of the values expected for undiluted standards. The manufacturer has validated the use of serum for lactate determinations instead of whole blood.

**Serum Myoglobin and CK-MB Determination**

Plasma or serum myoglobin, TnI, and CK-MB have been shown to be useful in evaluating cardiac muscle damage because of myocardial infarction. The time course for the appearance of each of these markers is known. Levels of cardiac TnI, the most specific marker for myocardial damage, peak at 12 to 24 hours, and may remain elevated for several days. Serum myoglobin becomes elevated within 2 to 4 hours of myocardial injury. CK-MB is found in cardiac and skeletal muscle but is present in much higher quantities in cardiac muscle. CK-MB levels become elevated within 3 to 4 hours of cardiac injury and remain elevated for 60 to 70 hours. Myoglobin and CK-MB can become elevated from noncardiac related injuries such as chronic muscle disease, skeletal muscle trauma, and renal failure. As a result, it is common to evaluate all three of these markers to determine the extent of cardiac and skeletal muscle injury.

Serum samples stored at -85°C were thawed once and tested for myoglobin (20 µL/well) and CK-MB (25 µL/well) using solid phase microplate sandwich enzyme-linked immunosorbent assays (Diagnostic Automation, Calabasas, CA). All samples and standards for these assays were performed in duplicate and averaged. Standard curves using four to seven reference standards of different concentrations were generated for each run. Myoglobin and CK-MB concentrations for the experimental serum samples were interpolated from these standard curves using best-fit regression formulas generated by Excel (Microsoft, Redmond, WA).

**Data Reduction and Statistical Analysis**

All data points represent means ± SEM for each parameter. Parametric statistics including two-way analysis of variance (ANOVA) or paired t-tests were used to compare quantitative data and groups. Trends were evaluated using linear regression. The experimental groups were compared against their own baseline and against the control group for each parameter (Prism v.3.03, GraphPad Software, San Diego, CA). Vital signs and blood chemistry values obtained for the animals that died within minutes of TASER discharge were not included in the statistical analyses.

**RESULTS**

**Vital Signs Were Severely Altered by TASER Discharge**

No spontaneous respiratory effort was observed during TASER discharge. An acute onset of tachycardia was noted after TASER discharge. Heart rate increased from a baseline of 103 bpm ± 9 bpm (mean ± SEM). The heart rate was greatest at the 5 minutes postdischarge time point (157 bpm ± 5 bpm; p = 0.0085 vs. baseline). Heart rate then gradually decreased during the remainder of the 60-minute monitoring period, but was not observed to return to the baseline until the 24-hour time point. At the 24-hour time point and subsequent time points, heart rates in experimental animals were similar to those of controls. The acute onset of tachycardia was not seen in control animals. Control animals showed a decrease in heart rate from baseline (91 bpm ± 2 bpm) during the initial 60-minute monitoring period with a nadir at 60 minutes (72 bpm ± 2 bpm; p < 0.05 vs. baseline). The observed effect on heart rate in the experimental group was significantly different from that of the control group when compared for the initial 60-minute monitoring time period by two-way ANOVA (p < 0.0001).

BP (Fig. 1) showed a decrease after TASER discharge in the first 60 minutes. BP reached a nadir at 15 minutes postdischarge (systolic BP = 79 mm Hg ± 8 mm Hg) in the experimental group. This decrease in systolic BP was significant (p = 0.02) compared with the baseline value (133 mm Hg ± 8 mm Hg) in the experimental group. The systolic BP gradually increased during the 60-minute monitoring period and returned to baseline values at 24 hours. BP did not show any significant changes in the control group. The difference observed between controls and experimental BP was significant (two-way ANOVA; p < 0.001).

**One Experimental Animal Died of Acute VF**

One animal in the experimental group (29 kg) died from VF after TASER discharge. Cardiac rhythm could not be discerned by EKG during the discharge because of the electrical interference and muscle contractions created by the TASER. Cardiac rhythm was evaluated by echocardiography during the discharge and found to be consistent with ventricular tachycardia. When the discharge ceased, sustained ventricular tachycardia was noted on echocardiography and confirmed by EKG (Fig. 2). During the course of the next few minutes, the ventricular tachycardia then degenerated into fatal VF. As previously indicated, all surviving experimental animals showed brief atrioventricular (AV) dyssynchrony followed by sinus tachycardia...
after the discharge. Despite persistent sinus tachycardia, no EKG evidence of acute dysrhythmia was seen in the surviving animals.

Echocardiography (echo) showed capture of the ventricular rhythm during TASER discharge but motion artifacts prevented quantitative analysis of cardiac output and ejection fraction. One animal, as described above, went into VF after the discharge as confirmed by EKG and echo. The remaining three animals all showed capture of ventricular rhythm with rapid ventricular contractions seen on echo consistent with ventricular tachycardia (approximate rate of 300 bpm). This capture of cardiac rhythm occurred immediately after the start and continued for the duration of the TASER discharge as seen by echo. Sinus rhythm was regained after a brief period of AV dyssynchrony in each of these three animals and sinus tachycardia began within 1 minute after termination of the discharge.

TnI (Fig. 3) showed an initial increase from baseline in the experimental animals at the 5-minute time point. A similar increase was also noted in control animals. TnI levels peaked at 24 hours postdischarge (0.052 ng/mL ± 0.03 ng/mL), this was not a significant increase from baseline values (0.02 ± 0.01, p > 0.05). No significant differences were seen when TnI values for experimental and control animals were compared using two-way ANOVA (p > 0.05). No significant changes were seen in CK-MB at anytime compared with that of controls.

**Severe Metabolic and Respiratory Acidosis was Seen After TASER Discharge**

Central venous blood pH (Fig. 4) showed a large decrease from baseline (7.45 ± 0.02) after the TASER discharge at the 5-minute time point (6.81 ± 0.07; p = 0.0004).
In the experimental group, central venous blood pH decreased throughout the 60-minute postdischarge monitoring session but returned to baseline values subsequently. Control animals had a similar baseline and showed no significant changes during the 72-hour monitoring period. The observed difference was significant when compared using two-way ANOVA during the initial 60 minutes ($p < 0.001$).

Extreme hypercapnia was noted after TASER discharge (Fig. 5). A dramatic increase in $P_{CO_2}$ was seen at 5 minutes (108.3 mm Hg ± 14.6 mm Hg) postdischarge. This change was in stark contrast to baseline values (45.3 mm Hg ± 2.6 mm Hg; $p < 0.0048$) for this group. The $P_{CO_2}$ gradually decreased during the 60-minute monitoring period, and returned to baseline at subsequent time points. Control animals had normal $P_{CO_2}$ values throughout the entire monitoring period. The difference observed between controls and experimental animals was significant (2-way ANOVA; $p < 0.001$).

Bicarbonate levels (Fig. 6) were found to be acutely and severely decreased from baseline values (30.8 mmol/L ± 0.9 mmol/L) at 5 minutes postdischarge (15.7 mmol/L ± 1.0 mmol/L; $p = 0.0046$). This decrease contrasted with the control group, which showed no significant changes in bicarbonate levels during the entire experimental time course. Bicarbonate levels remained decreased throughout the initial 60-minute postdischarge monitoring period and returned to baseline subsequently. When compared with controls over time, the observed changes in bicarbonate were significant (2-way ANOVA; $p < 0.001$).

Lactate values (Fig. 7) increased more than 13-fold after TASER discharge. Lactate levels increased from the experimental baseline of 1.6 mmol/L ± 0.3 mmol/L to 22.1 mmol/L ± 1.5 mmol/L ($p < 0.0001$) at 5 minutes postdischarge. Lactate levels remained elevated throughout the initial 60-minute monitoring period and returned to baseline values at 24 hours postdischarge. Control animals did not show any significant changes in lactate levels. Lactate levels in the control and experimental groups were significantly different when compared for the initial 60-minute monitoring time period (2-way ANOVA; $p < 0.001$).

Central venous oxygen saturation (Fig. 8) for the control and experimental groups was not significantly different at time 0 ($p = 0.70$). However, it decreased significantly after TASER discharge from the experimental baseline of 78.8% ± 4.6% at time 0 to 50.5% ± 5.8% at 15 minutes postdischarge ($p = 0.02$).
In the 46-kg animal, both 40-second discharges were administered with the TASER darts in the usual positions described in Methods. The first discharge resulted in immediate capture of ventricular rhythm resulting in ventricular tachycardia. Normal atrial contractions were noted during the discharge, but these contractions were not synchronized with ventricular contractions. When the discharge ceased, sinus rhythm resumed immediately. Similar cardiac effects to those seen in the first discharge were observed during the second 40-second discharge. At the end of the second discharge, sinus rhythm resumed immediately and sinus tachycardia was noted. This animal survived for 20 minutes without apparent ill effects at which time it was euthanized. For both animals, the cardiac activity directly visualized by thoracotomy was consistent with that seen by echocardiography.

**TASER Discharge had Moderate Affects on Potassium, Sodium, and Creatinine Levels**

Potassium values increased slightly in all animals from baseline to 5 minutes postdischarge. This increase was seen in both controls and experimental animals. The observed increase in potassium concentration at 5 minutes (4.2 mmol/L ± 0.1 mmol/L) in experimental animals was significant when compared with baseline (3.7 mmol/L ± 0.1 mmol/L). Potassium levels in the control and experimental groups were significantly different (p = 0.0328), but the differences were not clinically significant. At no time point did potassium values fall outside the normal range in any of the animals.

Creatinine values did not change significantly after TASER discharge nor did they exceed normal levels in any of the experimental animals (range, 1.1–1.7 mg/dL). Sodium levels showed an acute increase at 5 minutes after TASER discharge. The sodium concentration increased from a baseline value of 141.0 mmol/L ± 1.2 mmol/L to 148.2 mmol/L ± 1.6 mmol/L (p = 0.0052) then gradually returned to baseline at the 60-minute time point. Control animals showed a small decrease from baseline (138.3 mmol/L ± 4.8 mmol/L) at 5 minutes postdischarge (135.7 mmol/L ± 3.8 mmol/L; p > 0.05) and return to baseline at 60 minutes postdischarge. The observed difference between control and experimental animals in sodium concentration was significant when compared for the 60-minute postdischarge time period (2-way ANOVA; p < 0.0001).

**TASER Discharge Moderately Affected Serum Myoglobin**

Mean serum myoglobin levels in the experimental group at 30 minutes postdischarge (25.9 ng/mL ± 3.2 ng/mL, p = 0.0082) were elevated when compared with baseline (12.7 ng/mL ± 1.9 ng/mL). However, during all time periods, myoglobin levels in the control and experimental groups were not significantly different (2-way ANOVA; p > 0.05). All other values were within normal limits and variations were not of clinical significance.
DISCUSSION

Case reports, autopsies, and retrospective analyses have suggested that EID discharge may be associated with fatal dysrhythmias in humans, although the occurrence of this complication is rare. The dart placement chosen for the present study, with the current path traversing the left thorax, may represent a worst-case type of configuration for cardiac consequences from an EID such as the TASER X26. Our results show that during TASER discharges with this transcardiac vector there is a highly reproducible capture of cardiac rhythm producing ventricular tachycardia. Postdischarge effects included AV dyssynchrony and sometimes cardiac rhythm producing ventricular tachycardia. Postdischarge effects included AV dyssynchrony and sometimes fatal VF.

Echocardiography showed that cardiac rhythm was unmistakably affected during every TASER discharge studied. Rapid or immediate onset of atrial standstill, ventricular tachycardia, or VF occurred during these discharges. This study is the first to show the effects of the TASER X26 on the myocardium during thoracic discharges using a combination of echo, thoracotomy, and EKG. Our observations are in general agreement with those of Nanthakumar et al., who showed, using intracardiac EKG monitoring, that an unmodified TASER X26 can capture myocardial rhythm resulting in high rates of ventricular stimulation and potential dysrhythmia.

In two of eight animals exposed to TASER discharge, one with and the other without thoracotomy, the capture of cardiac rhythm and ventricular tachycardia were followed by VF and death. These animals had not been exposed to TASER discharges previously, showed no pre-existing electrolyte abnormalities and displayed no other physiologic abnormalities before the TASER discharges. The experimental conditions used for each of these animals differed somewhat. One animal had undergone a thoracotomy and had been anesthetized with inhaled anesthesia, whereas the other animal did not undergo thoracotomy and had been anesthetized with intravenous ketamine and xylazine. It could be argued that inhaled anesthesia reduces the threshold for VF and thoracotomy provides an atypical, more direct current path to the heart; however, neither of these conditions existed in the second case and fatal VF was seen nonetheless. It is possible that VF is a direct result of the current vector in combination with cardiac capture during the vulnerable period of ventricular repolarization (T-wave). Stimulation of the myocardium during this period has long been recognized as a cause of sustained ventricular dysrhythmia and sudden death. The frequency of the TASER wave form (19 Hz) makes it highly likely that one or more pulses will occur during T-waves even with brief discharges (1–5 seconds), yet sudden death is very rarely seen subsequent to TASER discharges in humans. The mechanism whereby these discharges capture cardiac function clearly requires further study.

McDaniel et al. showed that the threshold for VF with EID discharges was directly proportional to body mass for animals ranging from 30 to 117 kg. They also reported that the output of their custom-built TASER-like device had to be increased by a factor of 15 to induce VF with a 5-second discharge in 30 kg swine. Our animals varied in mass from 22 to 46 kg and two animals (29 kg and 31 kg) showed fatal VF after two 40-second discharges. If an unmodified TASER X26 has the same safety factor as that reported by McDaniel et al., then we should never have seen VF.

Webster et al. showed that discharges from a standard TASER X26 can cause VF and that the distance of the current emitting dart from the heart is a determining factor. The darts used here were placed with consistent reference to anatomic landmarks but the specific dart-to-heart distances were not measured. However, the approximate dart-to-heart distances (5–10 cm from the superior dart to the right ventricle and twice this from the inferior dart to the right ventricle) greatly exceeded the average distance of 1.5 cm and the maximum distance of 2.4 cm to the right ventricle where VF was reported by Webster et al. To some extent, this may be related to the thinner body wall and smaller thoracic dimensions in our animals (22–46 kg) when compared with those (54–74 kg) used by Webster et al.

In addition to direct electrical disruption of cardiac rhythm, it has been postulated that deaths associated with EID exposure may result from cardiac instability related to EID-induced lactic acidosis. Acidosis at pH <7.20 can lower the VF threshold, cause hyperkalemia, and reduce cardiac output. The profound metabolic and respiratory acidosis observed here was caused by the extreme degree of repetitive, global skeletal muscle contraction, by apnea, or by severe circulatory dysfunction.

In this regard, our findings concur with those of Jauchem et al., where TASER X26 discharges in anesthetized swine caused severe acidosis (pH <7.0) accompanied by dramatic hypercapnia (Pco2 >100 mm Hg) and elevated lactate (>15 mmol/L). It is known that when swine are exercised to exhaustion, large increases in lactate (>15 mmol/L) and resultant decreases in bicarbonate are seen. These metabolic changes from exhaustive exercise are countered in conscious swine by hyperventilation and resultant decreases in Pco2. In the Jauchem et al. study, acidosis may have arisen from inadequate spontaneous respiration and a lack of mechanical ventilation. In the present study, all animals were mechanically ventilated except during the two 40-second actual or sham discharge intervals. Immediately postdischarge, the respiratory rate was adjusted upward to meet the minute ventilation demand of each animal. Despite this intervention, clinically significant respiratory and metabolic acidosis persisted after the two 40-second TASER discharges but not after sham discharges.

The combination of severe hypercapnia and acidosis in the presence of hypotension indicates that circulatory function was affected by TASER X26 discharges. The hypercapnia seen in venous samples is similar to that seen with patients in cardiac arrest.
Effects of TASER Discharges

effectively, the tissues will continue to consume oxygen and produce CO₂. The result is a rise in venous CO₂, accompanied by a drop in venous oxygen saturation. The degree of hypercapnia seen in this study is well beyond that which would be expected in the setting of vigorous muscle contraction alone. The blood gas data observed here suggest that circulatory function was severely affected by the TASER discharge and this is confirmed by the observed decrease in BP. Similar cardiac effects were also seen by Nanthakumar et al., who showed a loss of BP in swine during TASER discharge measured by aortic manometry.

Two cardiac markers, CK-MB and TnI, were assayed here to assess myocardial injury. There were no elevations in CK-MB. TnI showed small, nonsignificant elevations in both the experimental and control groups. The induction and prolonged anesthesia sessions (2–3 hours) employed on the first day of the experiment may have evoked cardiac stress that contributed to these minor elevations in TnI. Anesthesia, especially at induction, is a known cardiac stressor, which results in an increased risk of adverse cardiac events. The present study has examined the effects of the TASER X26 using thoracic discharges with a transcardiac vector in anesthetized healthy swine. It does, however, have some limitations. (1) The number of animals used was relatively small but was counter-balanced by the high inter-animal reproducibility of the results. (2) For ethical reasons, ketamine/xylazine anesthesia was used in this swine model. Anesthesia precludes pain perception, which is one of the two principal effects of TASER discharges in conscious humans. Pain perception would undoubtly alter some of the responses reported here. (3) Only one vector of discharge (transcardiac) was utilized. Alternate discharge vectors may result in greater or lesser myocardial capture. In the field, TASERs are used to subdue combative individuals who are usually in a state of greatly increased sympathetic activity and, in many cases, are under the influence of alcohol or other drugs, which may alter the thresholds for dysrhythmia and for pain. Under those conditions, the effects of TASER discharge might deviate considerably from those seen here. (5) Only two 40-second discharges were used here. These lengthy discharges may have contributed to the incidence of VF, but Webster et al. used 5-second discharges and still observed VF.

The results of this study are in accordance with other published animal studies that have used standard, law enforcement-grade TASER X26 devices to study effects in swine. However, they are at variance with those obtained using custom-built TASER-like devices. In this swine model, lengthy thoracic discharges from a TASER X26 produced a reversible cardiorespiratory dysfunction which, when coupled with intense muscle contractions, resulted in severe acidosis, tachycardia, hypotension, and sometimes fatal VF. The cardiac capture and VF reported here may be facilitated by the vector of the current, the proximity of the emitting probe to the heart, or the temporal relationship of the discharge pulses to the vulnerable phase of the heart. This model of thoracic TASER discharge indicates that risk of cardiac dysrhythmia exists when the heart is interposed between the darts.

ACKNOWLEDGMENTS

We thank the staff of the Animal Facility for their assistance, the Des Plaines Illinois Police Department, and the Northern Illinois Police Alarm System (NIPAS) for their cooperation in providing essential material for this study.

REFERENCES


The Protective Effect of the Blood Brain Barrier From Systemic Cytokines in an Animal Femur Fracture Model

Mickey Ott, MD, Alan T. Davis, PhD, Wayne VanderKolk, MD, James H. Resau, PhD, David H. DeHeer, PhD, Clifford B. Jones, MD, Chad Stouffer, MD, and Edward W. Kubek, PhD

Background: Previous studies of head trauma have shown profound release of cytokines in the brain. These changes were not expressed in peripheral tissues. The intent of this study was to take an animal model of femur fracture, monitor the expression of biochemical markers in the periphery, and compare this to their expression in the brain.

Methods: Rats were subjected to a weight-drop, femur fracture model, and then killed at various times. Samples of muscle, liver, serum, and brain were analyzed for concentrations of cytokines, and compared with controls.

Results: Statistically significant (p < 0.05) results from the study were found in the liver. Interleukin (IL)-2, IL-10, IL-11, and other acute phase reactants were elevated at 24 hours after injury, compared with in controls. Analysis of these cytokines in the brain showed no significant increase when compared with those of controls. Further analysis also demonstrated an increase in plasma C-reactive protein and leptin in the fracture group. These results differ from our previous brain trauma study, which demonstrated no increased expression of cytokines in liver or plasma.

Conclusions: This animal model of peripheral injury demonstrates that there is a significant rise in acute phase reactants in liver tissue and plasma within 24 hours after injury, without a corresponding rise in cytokine concentration in the brain. These results suggest that although the brain is potentially exposed to the biochemical response to injury, the brain parenchyma itself is protected from up-regulation of proinflammatory cytokines. Interestingly, this is the opposite effect seen in our isolated brain injury study.

Key Words: Blood brain barrier, Cytokine expression, Rat model, Peripheral injury.

Plasma cytokines, hormones, and other growth factors were analyzed by Rules Based Medicine (Austin, TX). The metabolites measured included apolipoprotein A1, CD40, CD40 ligand (CD40L), epidermal growth factor, endothelin-1, eotaxin, factor VII, fibroblast growth factor (FGF)-basic, FGF-9, fibrinogen, granulocyte chemotactic protein (GCP)-2, growth hormone, immunoglobulin (Ig)A, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-11, IL-12p70, IL-17, IL-18, IP-10, leukemia inhibitory factor (LIF), lymphotactin, matrix metalloproteinase 9, granulocyte-macrophage stimulating factor, growth regulated protein-α (GRO/KC), interferon (IFN)-γ, monocyte chemotactic protein (MCP)-1, MCP-3, MCP-5, monocyte chemotactic and stimulating factor (M-CSF), Macrophage-derived chemokine (MDC), macrophage inflammatory protein (MIP)-1α, MIP-1β, MIP-1γ, MIP-2, MIP-3β, myoglobin, oncostatin M (OSM), regulated upon activation, normal T-cell expressed and secreted (RANTES), stem cell factor (SCF), serum glutamic oxaloacetic transaminase (SGOT), tissue inhibitor of metalloproteinase (TIMP)-1, tissue factor, thrombopoietin (TPO), vascular cell adhesion molecule (VCAM)-1, vascular endothelial growth factor, tumor necrosis factor-α (TNF-α), insulin, leptin, glucagon, glucagon-like peptide-1, C-reactive protein (CRP), and Von Willebrand’s factor. All of the preceding metabolites were measured in serum, brain, gastrocnemius muscle, and liver.

An aliquot of the serum was kept on ice and sent to the Van Andel Research Institute (Grand Rapids, MI), where it was analyzed using the VetScan Chemistry System (Abaxis, Union City, CA). The data to be retrieved from the sample included serum albumin, alkaline phosphatase, alanine aminotransferase, amylase, blood urea nitrogen, calcium, creatinine, globulin, glucose, potassium, sodium, total bilirubin, and total protein.

Data were analyzed as an analysis of variance. Significance was assessed at \( p < 0.05 \). If significant differences were found, the Fisher’s Protected Least Significant Difference test was run to determine differences between individual means. All analyses were conducted using the NCSS 2004 (Number Cruncher Statistical Systems, Kaysville, UT).

**RESULTS**

The results are summarized in Tables 1 and 2. Examples of both proinflammatory mediators and anti-inflammatory mediators in liver and their change in concentration over time are demonstrated in Figures 2 and 3. Of note, there was no effect of the fracture upon alterations in the serum electrolytes or liver function tests (LFTs) (data not shown).

**Liver, Brain.** The most interesting and statistically significant results came from our analysis of acute phase reactants in liver tissue samples. The concentrations of IL-2, IL-10, IL-11, leptin, IL-3, IL-4, IL-7, IL-17, IL-18, insulin, inductible protein (IP)-10, MCP-1, MCP-3, and MIP-3β were significantly elevated at 24 hours after injury compared with those of the control groups. In contrast, analysis of these cytokines in the brain showed no significant increase when compared with those of controls.

**Plasma.** Further analysis also demonstrated a statistically significant increase in plasma CRP in the fracture group, compared with in the controls. A similar effect was noted for leptin and MCP-3. In contrast, there was no statistically significant increase in CRP, leptin, or MCP-3 concentrations in the brain when compared with those of the controls.

**Muscle.** The data for the gastrocnemius muscle showed no consistent pattern of difference between the fracture group and the control group (data not shown).

**DISCUSSION**

The literature is replete with studies that examine the response of cytokines in relationship to trauma. The concern is that the exuberant response of the cytokines can lead to secondary injury. Among the known mediators of inflammation in trauma are IL-1 and TNF-α, and these were previously tested in a rat model of traumatic brain injury. These were shown to be increased dramatically. Acute-phase reactants like these, including both proinflammatory and anti-
inflammatory mediators, can be produced by macrophages, monocytes, B and T lymphocytes, fibroblasts, endothelial cells, and enterocytes. The effects of proinflammatory cytokines in general cause fever, anorexia, increased adrenocorticotrophic hormone and cortisol production, systemic hypotension, neutrophilia, increased acute-phase reactants, decreased levels of iron and zinc, and thrombocytopenia to list just a few.10 For example, in traumatic brain injury, IL-1 is directly involved with neuronal degeneration, and this has been confirmed by

**Table 1** Selected Metabolite Concentrations in Liver and Brain in the Control and Fracture Groups at 24 h

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Control Liver</th>
<th>Fracture Liver</th>
<th>Control Brain</th>
<th>Fracture Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 (ng/g)</td>
<td>1.11 ± 0.16*</td>
<td>1.61 ± 0.14*</td>
<td>0.50 ± 0.11</td>
<td>0.50 ± 0.07</td>
</tr>
<tr>
<td>IL-3 (ng/g)</td>
<td>44.4 ± 4*</td>
<td>92 ± 11*</td>
<td>BD</td>
<td>BD</td>
</tr>
<tr>
<td>IL-4 (ng/g)</td>
<td>0.31 ± 0.05*</td>
<td>0.38 ± 0.04*</td>
<td>0.20 ± 0.04</td>
<td>0.20 ± 0.03</td>
</tr>
<tr>
<td>IL-7 (ng/g)</td>
<td>0.37 ± 0.09*</td>
<td>0.48 ± 0.07*</td>
<td>0.10 ± 0.06</td>
<td>0.12 ± 0.05</td>
</tr>
<tr>
<td>IL-11 (pg/g)</td>
<td>132 ± 23*</td>
<td>260 ± 22*</td>
<td>35 ± 20</td>
<td>32 ± 16</td>
</tr>
<tr>
<td>IL-17 (ng/g)</td>
<td>0.17 ± 0.04*</td>
<td>0.23 ± 0.03*</td>
<td>0.05 ± 0.03</td>
<td>0.06 ± 0.03</td>
</tr>
<tr>
<td>IL-18 (ng/g)</td>
<td>2.9 ± 0.5*</td>
<td>3.6 ± 0.4*</td>
<td>1.3 ± 0.4</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>Insulin (μIU/g)</td>
<td>20 ± 3</td>
<td>24 ± 4</td>
<td>8.1 ± 1.9</td>
<td>7.9 ± 1.7</td>
</tr>
<tr>
<td>Leptin (ng/g)</td>
<td>0.42 ± 0.09*</td>
<td>0.65 ± 0.08*</td>
<td>0.17 ± 0.06</td>
<td>0.15 ± 0.03</td>
</tr>
<tr>
<td>IL-10 (ng/g)</td>
<td>0.49 ± 0.04*</td>
<td>0.75 ± 0.07*</td>
<td>0.14 ± 0.03</td>
<td>0.27 ± 0.19</td>
</tr>
<tr>
<td>MCP-1 (ng/g)</td>
<td>0.28 ± 0.12*</td>
<td>0.42 ± 0.03*</td>
<td>0.13 ± 0.03</td>
<td>0.15 ± 0.05</td>
</tr>
<tr>
<td>MCP-3 (ng/g)</td>
<td>0.30 ± 0.08*</td>
<td>0.49 ± 0.08*</td>
<td>0.19 ± 0.03</td>
<td>0.22 ± 0.05</td>
</tr>
<tr>
<td>MIP-3β (ng/g)</td>
<td>0.86 ± 0.22*</td>
<td>0.99 ± 0.16*</td>
<td>0.40 ± 0.10</td>
<td>0.47 ± 0.05</td>
</tr>
</tbody>
</table>

Data for the 0 time point, and time points 1 h and 6 h are not shown. The data were analyzed using the one-way analysis of variance. For significant effects after the analysis of variance, the Fisher’s Protected Least Significant Difference (FPLSD) test was used. The data are all expressed as mean ± SD. Significance was assessed at p < 0.05.

* Metabolite values for a specific tissue are significantly different from one another.

**Table 2** Selected Metabolite Concentrations in Plasma and Brain in the Control and Fracture Groups at 24 h

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Control Plasma</th>
<th>Fracture Plasma</th>
<th>Control Brain</th>
<th>Fracture Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>0.13 ± 0.07* ng/mL</td>
<td>0.32 ± 0.08* ng/mL</td>
<td>0.17 ± 0.06 ng/g</td>
<td>0.15 ± 0.03 ng/g</td>
</tr>
<tr>
<td>MCP-3</td>
<td>0.19 ± 0.08* ng/mL</td>
<td>0.36 ± 0.02* ng/mL</td>
<td>0.19 ± 0.03 ng/g</td>
<td>0.22 ± 0.05 ng/g</td>
</tr>
<tr>
<td>CRP</td>
<td>1177 ± 137* μg/mL</td>
<td>1563 ± 177* μg/mL</td>
<td>19 ± 5 μg/g</td>
<td>23 ± 7 μg/g</td>
</tr>
</tbody>
</table>

Data for the 0 time point, and time points 1 h and 6 h are not shown. The data were analyzed using the one-way analysis of variance. For significant effects after the analysis of variance, the Fisher’s Protected Least Significant Difference (FPLSD) test was used. The data are all expressed as mean ± SD. Significance was assessed at p < 0.05.

* Metabolite values for a specific tissue are significantly different from one another.

**Fig. 2.** Liver and brain IL-2 concentration in the fracture and control groups. The data reflect the mean value for three rats at each time point. The values for the liver control and fracture groups at 24 hours are significantly different from one another p < 0.05 (*).

**Fig. 3.** Liver and brain IL-10 concentration in the fracture and control groups. The data reflect the mean value for three rats at each time point. The values for the liver control and fracture groups at 24 hours are significantly different from one another p < 0.05 (*).
intracerebroventricular injection of IL-1. Both intracerebroventricular injection and systemic injection of IL-1 receptor antagonist has been shown to attenuate this damage.\textsuperscript{11,12} The concern in our study was whether a model of isolated peripheral injury causing increased production of acute-phase reactants could duplicate the results in the brain seen when IL-1 was injected. We were also interested in whether cytokines induced by trauma could either cross the blood brain barrier, or more importantly and possibly more indirectly, cause the brain to exhibit those features we have seen in the past with brain injuries.

The large numbers of acute-phase reactants found to be elevated in our study, are a mixture of both proinflammatory and anti-inflammatory mediators. For brevity, a few examples of both proinflammatory and anti-inflammatory reactants are further discussed now. Among the many proinflammatory cytokines associated with traumatic injury, IL-2 and leptin were found to be elevated in liver tissue in this study. IL-2 stimulates the growth and differentiation of T-cells and is essential to humoral immunity. It has been shown to be initially elevated in trauma patients.\textsuperscript{13,14} Leptin is a hormone that has undergone intense investigation recently. It has been shown to be increased in infection and inflammation, is proinflammatory, and likely plays a significant role in host immune response.\textsuperscript{15}

One of the hallmarks of a cytokine response to injury is that there is also an anti-inflammatory response. Intuitively, if one were to say there is only minimal injury then there would be no need for any anti-inflammatory cytokines. Two anti-inflammatory cytokines were elevated in liver tissue in our study as well. Interleukin-11 is an anti-inflammatory cytokine that has been shown to inhibit synthesis of proinflammatory cytokines.\textsuperscript{16} IL-11 was also demonstrated to be increased in animal models of shock and sepsis, as well as in human subjects after trauma. Interleukin-10 is produced in the bloodstream by macrophages and monocytes and can inhibit the inflammatory actions of IL-1, IL-6, TNF-\textgreek{a}, and INF-\textgreek{y}.\textsuperscript{5,17} Plasma concentrations of IL-10 have been shown to be elevated in patients with sepsis, shock, and multiple injuries, and a correlation with injury severity has been reported. Elevations of these four acute phase cytokines, IL-2, IL-10, IL-11, and leptin, in this peripheral injury study would be expected.

CRP was found to be elevated in the plasma of the fracture group. CRP is an acute-phase response protein produced by hepatocytes after a variety of physiologic insults including trauma.\textsuperscript{17} It can be used as a marker for inflammation, but is nonspecific and does not correspond well to injury severity or outcomes. Elevation of this in the plasma of the femur fracture rats is also to be expected.

One question that stimulated this experiment was how can the patient with a devastating, high-energy injury isolated to the extremity have such a profound systemic effect, yet have a relatively mild neurologic effect? The brain is protected in part from circulatory factors by the blood brain barrier, and correspondingly is protected from the environment by the skull. Our hypothesis was that the blood brain barrier would also protect the brain parenchyma from a peripheral cytokine response. This is not to say that previous work, which has suggested that the cytokine inflammatory milieu is seen in the brain, is incorrect. The hypothalamus and other centers that modulate fever, anorexia, etc. clearly show that the brain is aware and affected by the cytokines in the periphery, and may even work to regulate them. Is that to say, though, that brain tissue is affected by these cytokines to begin producing them in the absence of primary injury? Our previous model showed the level of cytokine response to direct injury, and in this study, we explored the response both systemically and in the brain of an isolated injury model. The model of rat femur fracture provides an isolated injury, and is something commonly seen on the trauma service. It is high energy in that the amount of force to fracture the femur, given its relatively large diameter, is great. This model involves soft tissue as well as bone, and should provide a clinically significant injury for creating the cytokine response. This response is indeed what was observed. The response, more importantly, was significant. This injury model, however, in keeping with our hypothesis did not show a corresponding response in the brain tissue. Moreover, this brain response shows neither an increase in proinflammatory response nor an up-regulation of neuroprotective cytokine inhibitors.

One might argue that the injury was not severe enough to cause a meaningful cytokine response. This model, however, is similar to others in the past and is consistent with an injury pattern seen in the trauma population. The increase in both plasma and the liver proinflammatory and anti-inflammatory cytokines suggests that the model creates a significant injury to mimic that seen in the trauma population.

Finally, many studies have reported communication of peripheral cytokines with the central nervous system occurring across the blood brain barrier.\textsuperscript{18} The exact nature of this communication is not completely known, and may involve active transport across the barrier via receptors, via the vagus nerve, or perhaps through secondary mediators. In regard to trauma, this may also include breakdown of the blood brain barrier. Reyes et al. showed elevations of mRNA expression of TNF-\textgreek{a}, interleukin-1\textbeta, and intracellular adhesion molecule (ICAM)-1 in the brains of rats after a 70% total body surface area third-degree burn.\textsuperscript{19} They postulated that the blood brain barrier collapses secondary to cerebral up-regulation of inflammatory cytokines. In our study, however, there was no evidence of up-regulation of inflammatory or anti-inflammatory mediators in the brain, despite there being significant elevation of cytokines in the periphery.

In conclusion, we present a model of peripheral injury that demonstrates a significant acute phase response of both proinflammatory and anti-inflammatory cytokines. In accord with our hypothesis, none of these acute phase response
mediators were found to be elevated in brain tissue at 24 hours. This strongly suggests that the blood brain barrier protects the brain parenchyma from the systemic, and potentially damaging, cytokine response to peripheral injury. In the future, analyzing gene expression of these cytokines in the brain as well as in the periphery may further elucidate this relationship and strengthen our hypothesis.

REFERENCES
Hematopoietic Progenitor Cells Mobilize to the Site of Injury After Trauma and Hemorrhagic Shock in Rats

Chirag D. Badami, MD, David H. Livingston, MD, Ziad C. Sifri, MD, Francis J. Caputo, MD, Larissa Bonilla, BA, Alicia M. Mohr, MD, and Edwin A. Deitch, MD

**Background:** Trauma and hemorrhagic shock (T/HS) has been demonstrated to result in bone marrow (BM) suppression and the release of hematopoietic progenitor cells (HPC) into the peripheral blood in both human beings and experimental animals. HPC have also been identified in numerous end organs after T/HS and the ongoing loss of progenitor cells from the BM may play a role in posttraumatic BM suppression. We investigated the hypothesis that HPC will specifically migrate to sites of tissue trauma and that this process is exacerbated by hemorrhagic shock (HS).

**Methods:** Sprague-Dawley rats (250–400 g) sustaining a unilateral lung contusion (LC) secondary to a blast wave of a percussive nail gun, were subjected to either HS (MAP 40–45 mm Hg for 45 minutes) or sham shock (SS). Animals were killed at 3 hours, 3 days, and 7 days after resuscitation and the right and left lungs from each animal were processed separately and the uninjured left lung served as a control for comparison with the contused right lung. BM mononuclear cells from each individual lung and the femurs were isolated and plated (2 × 10⁶) in duplicate for granulocyte-macrophage colony-forming units (CFU-GM), erythroid colony-forming units (CFU-E), and erythroid burst-forming units (BFU-E) colony growth.

**Results:** At 3 hours, LC resulted in a significant increase in progenitor colonies able to be grown from the injured lung compared with from the uninjured lung (CFU-GM: 11 ± 1 vs. 5 ± 2, CFU-E: 12 ± 7 vs. 5 ± 3, CFU-E: 7 ± 1 vs. 3 ± 1 colonies per 10⁶ BM mononuclear cells; all p < 0.05). HS resulted in a significant increase of the number of colonies of all three cell types in both the uninjured and the contused lung (all p < 0.05). At day 3 after HS, BM progenitor growth remained suppressed whereas the number of cells recoverable from the lung returned toward baseline. By day 7, hematopoietic progenitor cell growth in the BM and the number of those cells able to be grown from the lung returned to levels observed in unmanipulated rats.

**Conclusion:** Unilateral LC results in the rapid mobilization of a significant number of HPC from the BM to the site of injury. BM function is maintained under this condition. The addition of HS increases HPC mobilization from the BM and sequestration at the site of injury as well as decreasing BM HPC growth. We postulate that the accumulation of progenitor cells in the injured tissue combined with an alteration of normal BM homing, as exemplified by the decrease in progenitor cells from the lung without restoration of BM function, plays a role in posttraumatic BM suppression. The mechanism of shock-mediated mobilization from the BM and the exact role and fate of these cells at the site of injury requires further investigation.

**Key Words:** Hematopoietic progenitor cells, Homing, Hemorrhagic shock, Lung injury, Bone marrow.

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David H. Livingston, MD, FACS, University Hospital M234, Division of Trauma, Newark, NJ 07103-2406; email: livingst@umdnj.edu.
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increased number of HPC from the BM. We hypothesize that normal homing of circulating progenitor cells is disrupted by HS and trauma further contributing to BM suppression. The goal of this study was to determine the effect of lung contusion (LC) and HS on mobilization and homing of HPC from the BM to the site of injury.

**MATERIALS AND METHODS**

**Animals**

Male Sprague-Dawley rats (Charles River, Wilmington, MA), weighing 300 to 400 g, were housed under barrier-sustained conditions and kept at 25°C with 12-hour light/dark cycles. The rats had free access to water and chow (Teklad 22/5 Rodent Diet W-8640, Harlan Teklad, Madison, WI). All rats were maintained in accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals. The New Jersey Medical School Animal Care and Use Committee approved all animal protocols.

**LC and HS**

Briefly, rats were weighed and anesthetized with intraperitoneal sodium pentobarbital (50 mg/kg). Using aseptic techniques, the femoral vein and femoral artery were isolated and cannulated with polyethylene tubing (PE-50 and PE-10, respectively) containing 0.1 mL heparinized saline (10 units/mL). Both catheters (femoral vein and femoral artery) remained in situ for up to 3 hours after resuscitation. Then, the femoral artery catheter was attached in line to a blood pressure monitor (BP-2 Digital Blood Pressure Monitor, Columbus Instruments, Columbus, OH) for continuous blood pressure monitoring.

An LC was induced by using a blast wave of a percussive nail gun (Craftsman 968514 Stapler, Sears Brands, Chicago, IL) applied to a 12-mm small metal plate placed on the right axilla of the rat. This model has been shown to produce a clinically relevant LC as demonstrated by radiography and histology. The addition of HS results in a significant 50% decrease in PaO2 in the injured animal.12

Animals were allowed to recover from the LC until their heart rate and blood pressure stabilized, approximately 15 minutes, and then were randomly allocated to either HS or sham shock (SS) as previously described.12 Hemorrhagic shocked rats underwent blood withdrawal until the mean arterial pressure was reduced to 40 mm Hg. This pressure was maintained at this level for 45 minutes by withdrawing or reinfusing shed blood (kept at 37°C) as needed. Rectal temperature was monitored throughout the shock period and maintained at approximately 37°C by using an electric heating pad under the surgical platform. At the end of the shock period, animals were resuscitated by reinfusing all the shed blood at 1 mL/min. Sham shocked animals had placement of the indwelling catheters but did not undergo blood withdrawal. Overall operative mortality is 10% to 15% and was unaffected by pulmonary contusion. Animals were killed at 3 hours, 3 days, or 7 days after the resuscitation from sham or shock period. At the time of euthanization, the right (contused) lung, left (uninjured) lung, and bilateral femurs were harvested for progenitor cell assay.

**Hematopoietic Progenitor Cell Cultures**

The right and left lungs were processed separately. Lungs were mechanically shredded using two 18-gauge needles in 5 mL of cold MEM-alpha medium (Sigma Chemical, St. Louis, MO). BM was obtained by flushing each femur with 5 mL of cold MEM-alpha medium to ensure cell separation. Both lungs and femurs were centrifuged at 1,500 rpm for 15 minutes and suspended in RPMI 1640 (Sigma) containing 10% fetal calf serum (Hyclone Laboratories, Logan, UT). Lung or BM mononuclear cells (2 x 109) were plated in duplicate in Iscoves media containing 30% fetal calf serum, 2% bovine serum albumin, 1% methylcellulose, rat growth factor, penicillin/streptomycin (GIBCO, Grand Island, NY), 2 x 10-4 mol/L 2-ME, and glutamine (Cellgro; Mediatech, Herndon, VA), supplemented with 1.3 U/mL rhEpo and 6 U/mL rhIL-3 (Genetics Institute, Cambridge, MA) for BFU-E/CFU-E or 3 U/mL rhGM-CSF for CFU-GM. Cultures were incubated at 37°C in 5% CO2. BFU-E colonies were counted at day 7, CFU-GM at day 10, and BFU-E at day 15 by an observer who was blinded to the origin of the samples.

**Statistical Analysis**

Data are represented as mean ± SD. All data were subjected to univariate analysis and frequency table generation. Because of the small sample sizes, nonparametric techniques, including Mann-Whitney U test for bivariate analyses and Kruskal-Wallis H test for three or more groups were performed. The data were analyzed using SPSS 14.0 (SPSS, Chicago, IL). A p value of <0.05 was considered significant.

**RESULTS**

**BM**

HS and LC resulted in a significant decrease in BM CFU-GM, CFU-E, and BFU-E compared with the sham shocked-LC animals (Fig. 1). This data are consistent with our previous results in rats undergoing laparotomy and HS.3,13 In shocked rats, BM hematopoietic progenitor cell growth for all three cell types remain significantly below that in sham treated animals on day 3 (Table 1) but fully recovered by day 7. These data are also consistent with previous reports from our laboratory.13

**Lung**

The effect of LC alone is seen in Figure 2. The numbers of progenitor cell growth colonies from the uninjured left lung of the sham shocked animals were 5 ± 2 for CFU-GM, 5 ± 3 for CFU-E, and 3 ± 1 for BFU-E. In contrast, there was a marked increase in progenitor cell number in the contused right lung: 11 ± 1 for CFU-GM, 12 ± 7 for CFU-E, and 7 ± 1 for BFU-E. The increase in all cell types is significant. Of
note, normally only ≤2 colonies of HPC are recoverable from naive uninstrumented animals indicating that there is likely some transmitted effect of the chest wall impact to the left lung. Nevertheless, the left lung appears grossly and histologically normal and the increase in the number of HPC able to be cultured from the injured right lung is significant. These data indicated that isolated tissue injury both induces BM HPC mobilization as well as is a site or sequestration of circulating BM HPC.

Table 1 BM Hematopoietic Progenitor Growth Over Time

<table>
<thead>
<tr>
<th>Time</th>
<th>CFU-GM</th>
<th>CFU-E</th>
<th>BFU-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>36 ± 7</td>
<td>10 ± 4*</td>
<td>51 ± 13</td>
</tr>
<tr>
<td>3 d</td>
<td>51 ± 13</td>
<td>16 ± 4*</td>
<td>49 ± 9*</td>
</tr>
<tr>
<td>7 d</td>
<td>73 ± 7*</td>
<td>73 ± 3*</td>
<td>74 ± 17*</td>
</tr>
<tr>
<td>Shock</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>14 ± 3*</td>
<td>21 ± 11*</td>
<td>39 ± 13</td>
</tr>
<tr>
<td>3 d</td>
<td>21 ± 11*</td>
<td>21 ± 8</td>
<td>83 ± 9*</td>
</tr>
<tr>
<td>7 d</td>
<td>74 ± 17*</td>
<td>70 ± 6*</td>
<td>68 ± 7*</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD colonies per 1 × 10⁶ BM cells. *p < 0.05 vs. sham at same time point. † p < 0.05 vs. 3 hours.

HS resulted in an increased mobilization and trapping of HPC in the contused and uninjured lung (Figs. 3 and 4). Shock resulted in a threefold increase in the colony growth in both the contused and uninjured lung. Again, all three cell types were affected equally.

To further assess the impact of LC and HS on the mobilization of HPC, we analyzed data as the total number of HPC present in the lung. Because of the area of hemorrhagic contusion in the right lung as well as the difference in the number of lobes between the right and left lung, comparisons between contused uninjured lungs have greater variability than comparisons of the same lung across treatment groups. Nevertheless a similar pattern emerges (Table 2) and the impact of HS on the sequestration of HPC in the lung at 3 hours is magnified compared with the data when expressed as colonies per plate.

Lung progenitor cell growth decreased significantly over time (Table 3). Three days after resuscitation from HS, progenitor cell growth was one-third of what it was at 3 hours. At this time period, however, BM progenitor growth had not made any recovery (Table 1). CFU-E and BFU-E colony growth from the lung demonstrated a similar time-related pattern (data not shown).
Lung at 3 hours progenitor cells have been shown to be capable of giving rise to lungs). Recently, in experimental models, BM stem cells may be a mechanism by which damaged tissues are repaired.16 Recently, in experimental models, BM stem cells have been proposed that BM stem cell migration into sites of injury is the proteolysis of the BM stromal matrix. Trauma and inflammation have been shown to result in an exaggerated release of elastase from neutrophils and an induction of serine proteases. Elastase and serine proteases are involved and required for HPC mobilization.21 In addition, Winkler et al. showed that the expressions of naturally occurring serine protease inhibitors are decreased during BM cell mobilization.21 Another possible mechanism for the increased egress of HPC from the BM is the loss of adhesion molecules on the progenitor cells for endothelial cells in the marrow sinusoids, which allows their increased migration across the endothelium and extracellular matrix barrier.22

The constitutive release and circulation of a small population of BM hematopoietic cells are a part of the normal steady state homeostatic process of host defense and tissue repair. In normal adults, BM progenitor cells continuously migrate from the BM to the blood and back to the BM in such a way that circulating stem cells are always available in the peripheral blood to open BM niches.14 This process can be clinically manipulated by repeated injections of G-CSF to cause exaggerated stem cell mobilization for use in BM transplants. In addition, chemotherapy, radiation, as well as inflammatory states have been demonstrated to trigger an imbalance in the steady state circulation of BM HPC leading to an increased number of these cells in the periphery.15 It has been proposed that BM stem cell migration into sites of injury may be a mechanism by which damaged tissues are repaired.16 Recently, in experimental models, BM stem cells have been found to home to areas of ischemic myocardium and it has been proposed that these cells participate in myocardial repair.17-19 Lagasse et al. have shown that BM stem cells are capable of giving rise to hepatocytes18 and early progenitor cells have been shown to be capable of giving rise to a number of distinct cell lineages.20

Our previous work in both human beings and experimental animals has demonstrated that T/HS induces an exaggerated and prolonged mobilization of HPC to the periphery. Simultaneously, T/HS results in multiple organ dysfunction, including BM hematopoietic failure. The data presented here demonstrate that isolated soft tissue injury (LC) results in the early release of BM HPC, which preferentially sequesters into the damaged tissue. The addition of HS exaggerated the mobilization of the HPC to the damaged tissue and resulted in significant and prolonged BM suppression. Of note, there is a marked decrease in the ability to grow progenitor from the injured lung on day 3 at the same time that significant BM suppression still exists. Thus, our data would suggest that BM dysfunction after shock and trauma involves several mechanisms, including the increased mobilization of cells from the BM, trapping of these cells by injured tissue, and the failure of the cells to home back to the BM.

T/HS affects numerous end organs including the BM, and the mechanisms and factors that are involved in this process are not well understood. Normal hematopoiesis requires the cooperation and regulation of several cell types and factors within tightly controlled niches. It is likely that the egress of the HPC measured in this study is just one of the effects of HS on the BM microenvironment. One possible mechanism for the increased loss of BM cells to the periphery is the proteolysis of the BM stromal matrix. Trauma and inflammation have been shown to result in an exaggerated release of elastase from neutrophils and an induction of serine proteases. Elastase and serine proteases are involved and required for HPC mobilization.21 In addition, Winkler et al. showed that the expressions of naturally occurring serine protease inhibitors are decreased during BM cell mobilization.21 Another possible mechanism for the increased egress of HPC from the BM is the loss of adhesion molecules on the progenitor cells for endothelial cells in the marrow sinusoids, which allows their increased migration across the endothelium and extracellular matrix barrier.22

The data presented here clearly demonstrate that several types of HPC are recruited into an area of tissue injury. Abe et al., using a novel parabiotic crossed circulation model, demonstrated that BM cells were involved in tissue repair using a chemical lung injury model.23 They also found that tagged BM cells homed and then differentiated into fibroblast-like interstitial cells as well as type I alveolar epithelial cells. The signals leading to increased sequestration of HPC to the lung are not fully known; however, increased expression of numerous cytokines has been shown in injured tissue in both human beings and experimental animals and may be involved in the recruitment process. Hoth et al., in a rodent open pulmonary contusion model showed that the injured lung had increased levels of the chemoattractants cytokine-induced neutrophil chemoattractant-1 (CINC-1) and macrophage-inflammatory protein-2α (MIP-2α) as well as expression of intercellular adhesion molecule-1 (ICAM-1) and Interleukin-1 (IL-1).24 Hauser et al. showed that fluid surrounding the sites of fracture in trauma patients contained high levels of IL-6 and IL-8,25 and Rojas et al. showed an increased expression of interferon-γ (IFN-γ), IL-2, IL-1β, and IL-4 in the lung 14 days after bleomycin-induced lung injury.26 Along with an increase in local tissue cytokine levels, adhesions molecules and integrin expression may be upregulated at the site of injury, which may facilitate the trapping of circulating progenitor cells, whereas a loss of these molecules within the

### Table 2 Hematopoietic Progenitor Cell Colonies per Lung at 3 hours

<table>
<thead>
<tr>
<th></th>
<th>Sham Shock</th>
<th>Hemorrhagic Shock</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Uninjured</td>
<td>Contused Lung</td>
</tr>
<tr>
<td>CFU-GM</td>
<td>37 ± 24</td>
<td>101 ± 43*</td>
</tr>
<tr>
<td>CFU-E</td>
<td>40 ± 24</td>
<td>110 ± 65*</td>
</tr>
<tr>
<td>BFU-E</td>
<td>21 ± 19</td>
<td>64 ± 41*</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD colonies per lung. 
* p < 0.05 (uninjured SS lung vs. contused SS lung). 
† p < 0.05 (contused HS lung vs. uninjured HS and contused SS lungs).

### Table 3 Lung CFU-GM Progenitor Growth Over Time

<table>
<thead>
<tr>
<th></th>
<th>Sham Shock</th>
<th>Hemorrhagic Shock</th>
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<tr>
<td></td>
<td>Uninjured</td>
<td>Contused Lung</td>
</tr>
<tr>
<td>CFU-GM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>5 ± 1</td>
<td>11 ± 1*</td>
</tr>
<tr>
<td>3 d</td>
<td>4 ± 3</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>7 d</td>
<td>2 ± 2</td>
<td>1 ± 1</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD colonies per plate. 
* p < 0.05 vs. day 7.
BM drives the cells into the periphery.27–29 Because these cells were able to be recovered in the injured lungs of the SS animals, it is likely that the mobilization of these cells to the site of injury may be involved in tissue repair. In contrast, because acute lung injury is a prominent feature in patients sustaining HS complicating severe trauma, it remains a possibility that exaggerated numbers of BM HPC, which are mobilized to the lung cells observed in this group, may participate in posttraumatic pulmonary failure and increase the susceptibility to secondary infection.

In summary, the results of this study demonstrate that tissue injury alone is a stimulus to induce mobilization of progenitor cells from the BM to areas of tissue injury. These processes of mobilization and sequestration are exacerbated by HS, which also results in persistent BM suppression. These data parallel the observations of BM mobilization and suppression in human beings after severe injury and thus we think these findings are central to posttraumatic hematopoiesis dysfunction. In addition, as pulmonary dysfunction remains a common cause of morbidity after injury we postulate that exaggerated BM mobilization and sequestration may play a role in posttraumatic lung injury and wound healing. Further studies are ongoing to examine the final outcome of these tissue progenitor cells and their effect on local immunity, wound healing, and the susceptibility to subsequent infection.

REFERENCES


DISCUSSION

Dr. Richard L. Gamelli (Maywood, Illinois): Dr. Livingston’s group has advanced our understanding of the bone marrow response to injury in fundamentally important ways. This work today brings forth new findings that require, as the authors have pointed out, further analysis to truly understand the full implication of these observations.

I have the following comments and questions for the authors. The authors would be better served and able to
support their conclusion of hematopoietic cells in the lung remobilized from the BM if they employed florescent-tag BM progenitors.

Have you considered such a study to further cement your observations? Is it possible that the progenitors that were isolated from the lungs are due to demargination of cells due to injury-induced changes as a result of catecholamine release?

Our group, following up on the work of Mastrioni, has demonstrated burn-induced changes in hematopoiesis are, in part, related to catecholamines, as well as influencing BM derived within inflammatory cells.

I was somewhat surprised to find that the colony recovery from two million nucleated cells from the BM and lungs in the colony assay represented only a very small percentage of the plated cells that differentiated in response to specific growth factors.

Do you have an explanation? The authors could have used specific self-surface markers, such as CD-34, CD-117, or TUR-19 to obtain a better characterization of a distribution of progenitors in the study tissue beds. Although injury may have increased the number of HPC in the lung, are you convinced that the numbers are sufficient to support the notion that BM suppression was present as soon as 3 hours after injury?

What information do you have on the total number of HPC per marrow? The lung data were here, which is fairly good. Do you have similar numbers in the liver and the spleen?

Release of BM cells, although highly regulated, is still a leaky system. Along with fully differentiated cells, there’s always a release of immature cells of the different lineages in the different levels of differentiation into the periphery.

If so, is it possible that the lung injury simply provides the environment for the sequestration of some of these cells through chemokine and cytokine tissue levels that facilitate leukocyte sequestration into the injured area?

And finally, do you have any evidence that HPC homing is impaired under injury conditions; therefore, the HPC that have accumulated in the lung are incapable of homing back to the BM? I ask these questions, because our understanding of the basic mechanisms will be critical to knowing the importance of how we’re going to approach this as a problem, if at the end of the day, this is a major mechanism for hematopoietic failure, because we’ll have to be able to deal with this.

Dr. Chirag Badami (Newark, New Jersey): The first question you asked about was tagging BM cells.

Actually, we’re currently in the process of doing that. We’ve found a method to tag BM cells and plant them into the rat, have them undergo trauma hemorrhagic shock, and try to find out where they go and how long they’re present therefore.

So it was a good suggestion, and we are working on that. The second question you had was whether the catecholamine plays a role in sequestration of these BM cells. We just began this study, developed the model, and found these findings, and now we’re moving on to what causes these BM cells to sequester.

We’re also trying to figure out what causes these BM cells to leave. I know it’s a very complicated topic. I know there’s a lot of literature on it. But that’s our next step and that’s where we kind of want to go with that, along with tagging the BM cells and seeing what role they play in that area and how long they last.

We haven’t really talked about setting antibodies up for CD-34 cells or anything like that, but I think that’s a good suggestion. You also asked about hematopoietic pregen cells being impaired, returning back to the BM.

My project consisted of evaluating the study over time. And I did it after 3 hours, after 3 days, and after 7 days. The data wasn’t here, and it wasn’t presented today, but after 3 hours, we saw a pretty significant increase in cells in the lung.

At 3 days, we already see a decreasing of these cells in the lung. Now, we’re not sure whether they simply die, whether they change and differentiate into a different type of cell, or whether they return to the BM. We hope the fluorescence in tagging of the BM cells helps us in evaluating that.

By 7 days, pretty much no colonies grow out of our injured tissue. So, again, we think tagging the BM cells will help us answer that question.

Dr. Matt Delano (Gainesville, Florida): I have a couple of questions. You looked, you said, at 24-hours and it showed that the colony forming units had different lineages, which were depressed.

However, when you look at the BM in infection models of parasite and bacteria, you can see at 24-hours, although the granulocyte lineage is definitely decreased, there’s also an increase over the next 7 days in the myeloid lineage.

Although the granulocyte lineage is decreased, you can actually find evidence in the spleen and the liver that the colony forming units actually increase in those organs.

So, although there is early decrease in the BM, that’s made up for in the other peripheral organs, which you say you’re going to look at.

Ochoa and Ochoa have shown in other traumatic stress models in end cancer, that the immature myeloid cells in cancer models, called myeloid suppressor cells, actually are the precursors of dendretic cells and monocytes. And when grown in those cells with granulocyte-macrophage colony stimulating factor, those cells mature. Have you done those experiments, or do you plan to actually look at the function of these cells and move on from the descriptive studies of their accumulation from the BM to the organs?

Dr. Chirag Badami: Actually, we haven’t done studies where we give GCSF—we basically just focused on the trauma and hemorrhagic shock model. We haven’t used any other models. We haven’t used a cancer model, an infection model, or anything like that. Our research focus is purely on trauma and hemorrhagic shock.

We’re still in the preliminary stages. We took a long time in developing the model. We found these findings and we
developed these findings. So I think, in the future, that that’s a good suggestion, and then we’ll take a look into it, but for now, we haven’t really done that.

**Dr. Timothy R. Billiar** (Pittsburgh, Pennsylvania): I wonder how firm the conclusion is that the primary reason for the early BM failure is due to mobilization of the progenitor cells, versus the production of local factors within the BM that’s suppressive. And as an experimentalist, the experiment that comes to mind is the possibility of mixing the BM from the two sources to determine whether there’s an environment within the BM that’s suppressive.

Maybe that’s been done, and maybe you’ve done that, but I’d be interested in knowing the answer to that question.

**Dr. Chirag Badami:** Actually, we feel that the mobilization for gender cells may or may not contribute to BM failure. We’re not sure if that’s the reason the BM is failing. Obviously, we see it after trauma and hemorrhagic shock. We haven’t shown it just after injury itself.

I think it’s maybe a combination of the injury, along with the other factors that take place in the BM that causes this failure in this BM suppression. I think it’s a combination of all, but I don’t know if it’s purely, directly related just to our injury.

**Dr. Timothy R. Billiar:** Have you ever tried to mix the BM to see whether there are suppressive factors really early after trauma hemorrhage within the BM compartment?

**Dr. Chirag Badami:** We actually haven’t done that yet, but it’s a good suggestion I think.

**Dr. Rao R. Ivatury** (Richmond, Virginia): Can I also ask you to comment on multiple injuries, especially critical injuries with involvement of the lung; what do you anticipate under those circumstances, and how would you go about studying that?

**Dr. Chirag Badami:** Actually, when we continue this study, we want to evaluate other injuries. We want to evaluate liver injuries, we want to evaluate fractures.

I think we started off with the lung, because we had our internal control. We had the left side versus the right side, which allowed us to be flexible with this data.

But I think, as we further do this, we are going to evaluate other studies, and we think it will have a similar role. We think progenitor cells, no matter where the injury is, I think, will home to that area after trauma and hemorrhagic shock.

**Dr. Martin A. Croce** (Memphis, Tennessee): Just one quick thing—sort of as a mechanistic thing. Depending on the time of harvest for injured lung versus uninjured lung, be very careful, at least in a larger animal model. We noticed that the uninjured lung quickly became the injured lung due to secondary lung injury. So in your future work, be careful about the time interval between injury and harvest.

**Dr. Chirag Badami:** If you saw the picture, we do cardiopulmonectomy. We take the trachea, and we just follow it back down and both lungs come out at the same time.

**Dr. Martin A Croce:** I would suggest doing histology on the uninjured lung, because grossly, they look the same, but the uninjured lung is full of neutrophils.
Inhibition of Inducible Nitric Oxide Synthase Ameliorates Lung Injury in Rats After Gut Ischemia-Reperfusion

Kotaro Uchida, MD, Shiro Mishima, MD, Sho-ichi Ohta, MD, PhD, and Tetsuo Yukioka, MD, PhD

Background: Gut hypoperfusion is considered to be a critical event for organ failure during severe surgical insults. The mechanism of remote organ injury after intestinal ischemia-reperfusion (I/R) may involve the excessive nitric oxide (NO) production; however, its role has been controversial. We sought to determine whether a selective inducible NO synthase inhibitor, aminoguanidine (AG), ameliorates pulmonary microvascular injury after superior mesenteric artery occlusion.

Methods: Anesthetized rats underwent superior mesenteric artery occlusion for 30 minutes and reperfusion for 6 hours (I/R) or sham operation (control). Another set of animals undergoing I/R received an AG at the end of the ischemia. Pulmonary vascular permeability was assessed by measuring tissue retention of Evans Blue dye that binds albumin. The plasma was harvested and NO2/NO3 (end products of NO) was measured. The bacterial cultures of the mesenteric lymph nodes of animals were performed to estimate the gut bacterial translocation after injury.

Results: The concentration of NO2/NO3 of plasma in the I/R group was higher than that of the control (p < 0.05). The lung-to-plasma Evans Blue dye ratio in the I/R group was also higher than that of the control (p < 0.01). Treatment with the AG prevented this lung injury induced by the gut I/R. The incidences of gut translocation were not significantly different between the I/R and AG groups.

Conclusions: Increased lung vascular permeability elicited by gut I/R was significantly attenuated with inhibition of an inducible NO release by AG. Control of bacterial translocation was not needed to prevent lung injury in this model.

Key Words: Bacterial translocation, NO, Aminoguanidine, SMA occlusion.


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From the Department of Emergency and Critical Care Medicine (K.U., S.M., T.Y.), Tokyo Medical University; the Department of Emergency and Critical Care Medicine (S.O.), Hachiouji Medical Center, Tokyo, Japan.


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Address for reprints: Shiro Mishima, MD, Department of Emergency and Critical Care Medicine, Tokyo Medical University, 6-7-1 West-Shinjuku, Shinjuku, Tokyo 160-0023, Japan; email: manu9@mac.com.

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Shock associated with organ dysfunction causes inadequate systemic and regional perfusion and may be the common denominator linking these disparate causes. In particular, the gut is prone to a disproportionate splanchnic vasoconstriction, and the resulting ischemia-reperfusion (I/R) injury is thought to be the “motor” causing both local mucosal injury and remote organ failure. The reduction of mesenteric perfusion is associated with impairment of mucosal barrier function, which permits translocation of bacterial pathogens into splanchnic circulation. Subsequent reperfusion leads to further mucosal injury and induces systemic inflammatory reaction. These effects are clinically most relevant in the lung, where capillary leakage results in protein loss into the interstitium followed by transcapillary fluid shifts. These symptoms may progress to non-cardiogenic pulmonary edema or adult respiratory distress syndrome.

Studies of intestinal I/R linking the local process to the resulting systemic changes have identified nitric oxide (NO) as a potential mediator. However, the role of NO in the model is still controversial, and the literature is replete with studies reporting NO as being either beneficial or detrimental to I/R-induced injury. Current opinions concerned with this field pay attention to the relationships between the time course of insult and different forms of NO synthase (NOS), so-called constitutive and inducible NOS.

Clinical and experimental data indicate that elevated NO levels may be critically involved in both shock and endotoxin-induced gut injury, although the mechanisms by which it exerts its effects remain to be fully clarified. A group including one of the present authors (S.M.) previously demonstrated that the mucosal injury was associated with inducible NOS (iNOS) activity increase in an animal endotoxin challenged model. Therefore, prevention of iNOS activity and reduction of excess and prolonged NO production may be beneficial in endotoxin shock.

In this study, we used aminoguanidine (AG), a relatively selective iNOS inhibitor, and tested whether it ameliorated pulmonary injury after gut I/R. As a marker of lung edema, Evans Blue dye (EBD) leakage from plasma to organ interstitium was measured. This method is far more sensitive to microvascular dysfunction than lung weight. Initial work in this field assumed that the progression from intestinal I/R to acute lung injury was the result of bacterial translocation. We therefore also performed microbiologic assessment and examined the histology of the intestine.
MATERIALS AND METHODS

Materials and Animal Preparation

All reagents were obtained from Wako Chemical (Tokyo, Japan). Adult male Wistar rats (Saitama Experimental Animals, Saitama, Japan) weighing 250 g to 350 g were used. They were housed under barrier-sustained conditions and maintained according to the recommendations of the National Research Council guidelines for Care and Use of Laboratory Animals. The rats were fed standard laboratory chow (CE-2, Clea Japan, Tokyo, Japan) and water ad libitum. The Animal Care Committee of Tokyo Medical University approved the experiments.

Experimental Design

The goal of the experiment was to examine the relationships of NO among gut I/R, bacterial translocation, and acute lung injury. To accomplish this, animals were randomized into the following three groups (n = 6 each): (1) time-matched, sham-operated animals undergoing laparotomy under general anesthesia with 80 mg/kg of ketamine and 8 mg/kg of xylazine intraperitoneally and dissection of the proximal superior mesenteric artery (SMA) without occlusion served as the control group, (2) animals subjected to SMA occlusion with a microvascular clip for 30 minutes and reperfusion for 6 hours were the I/R group, (3) animals receiving I/R insult and administered 100 mg/kg of AG intraperitoneally at the end of the gut-ischemia period were in the AG group.

Quantitative Analysis of Pulmonary Injury

Pulmonary vascular permeability was assessed using EBD that binds albumin. EBD has been used as a marker of protein extravasations in models of inflammatory tissue injury. This technique compares favorably with the methodology of using radiolabeled albumin. During the gut-ischemia or sham operation period, 0.2 mL of 1.5% EBD was administered to the animals intravenously via the penile vein. After the reperfusion, the lungs and heart were excised under general anesthesia, and the pulmonary vasculature was cleared of blood by gently infusing saline solution into the right ventricle.

The lungs were then weighed and placed in 5 mL of 10% buffered formalin at 37°C overnight. The tissue was homogenized and centrifuged, the supernatant and the plasma was measured by means of spectrophotometry at 620 nm. The concentrations of EBD extracted from the lungs were divided by those of the plasma, and the values were expressed as the lung-to-plasma ratio as indicators of the lung injury.

Bacterial Translocation

We examined bacterial translocation to the mesenteric lymph nodes complex (MLNs) to estimate the gut mucosal injury. The MLNs were harvested and quantitated for translocating bacteria as previously described. Briefly, using sterile technique, the MLNs were excised, weighed, and homogenized in 0.5 mL of broth. Aliquots (0.2 mL) were plated onto blood and MacConkey agar plates. The plates were examined after 48 hours of aerobic incubation at 37°C. After the MLNs had been harvested, the cecum was removed, weighed, and homogenized. Serial dilutions of the homogenate of the cecum and luminal contents were plated onto blood and MacConkey agar plates to estimate cecal bacterial population levels.

Nitrite and Nitrate (NO₂⁻/NO₃⁻) Assay

Concentration of nitrite and nitrate, which are stable end metabolites of NO production in the plasma and lung, were measured for assessment of NO production. Small portions of the lung were removed, weighed, homogenized, and centrifuged at 3,000 rpm for 10 minutes. Cardiac (systemic) blood samples were collected in syringes containing 100 units of heparin and centrifuged to remove the cellular components. The tissue and plasma samples were stored at -20°C until the assays were performed.

NO₂⁻/NO₃⁻ levels were measured with the nitrate reductase and Greiss reagent (combination of equal amount of 0.2% naphthyl ethylenediamine dihydrochloride in water and 2% sulfanilamide in 5% H₃PO₄). Briefly, 100 µL of each sample was incubated for 30 minutes at 37°C in a 500 µL reaction volume containing 0.05 mol/L HEPES (25 µL), 0.005 mmol/L flavin adenine dinucleotide (25 µL), 0.1 mmol/L nicotinamide adenine dinucleotide phosphate (50 µL), and 0.1 U/µL nitrate reductase (10 µL).

After incubation, 5 µL L-lactic dehydrogenase and 50 µL of 100 mmol/L pyruvate were added to each sample tube. The tubes were incubated for an additional 10 minutes at 37°C, after which they were deproteinized with 30 µL of 30% ZnSO₄. Greiss reagent (500 µL) was added to each tube and after 10 minutes, the samples were read at 543 nm with a spectrophotometer. Sodium nitrite was used as the standard.

Histology

The terminal ileum specimens were harvested immediately after the animals were killed, and rinsed in cold saline with subsequent immersion in 10% buffered formalin overnight at room temperature. The tissue was then dehydrated and embedded in paraffin, sectioned and stained with hematoxylin and eosin. Each slide was evaluated in a blinded fashion by a separate investigator. Five random fields (100× magnification) were evaluated per animal. The incidence of ileal villous damage was determined by dividing the number of injured villi by the total number of villi examined.

Statistical Analysis

All results were expressed as means ± SD. Translocation incidence (discontinuous data) was evaluated by χ² analysis with the Yates’ correction. Continuous data were analyzed by one-way analysis of variance using the post hoc Newman-Keuls test when comparing the different groups. Probabilities <0.05 were considered significant.
RESULTS

No animals died during the I/R period. The control had no bacterial translocation to the MLNs (Table 1). Both the I/R and AG groups demonstrated positive bacterial cultures in the MLNs after the gut I/R insult, with no statistical difference in incidence and magnitude. The cecal bacterial population levels did not significantly differ among any of the groups (Table 1).

Consistent with the previously reported studies in the gut I/R model,13 the nitrite and nitrate concentration after I/R increased significantly in the lung and plasma (Table 2). The AG prevented the NO production increase of the plasma compared with that of the I/R.

The lung-to-plasma concentration ratio of EBD increased after the SMA occlusion compared with that of the control (Table 3). The ratio in the AG group was not different from that of the control, significantly. Inhibition of iNOS activity with AG prevented the capillary leakage increase significantly.

Gut I/R-induced mucosal injury was associated with histologic changes manifesting as edema of the lamina propria and the subepithelial space (Fig. 1). The heights of villi were decreased in the injured mucosa. The light microscopy appearances of the ileum showed mucosal injury both in the I/R and AG group. The incidence of ileal mucosal damage were similar both in the I/R and AG group (Table 4).

DISCUSSION

During the last decade, evidence has accumulated suggesting that loss of the gut mucosal barrier plays a role in the development of sepsis, postinjury hypermetabolism, and distant organ injury.14 Consequently, a large number of studies have been conducted investigating potential mechanisms by which diverse insults could impair intestinal mucosal barrier function and promote bacterial translocation. One area of particular interest is the relationships among endotoxemia, intestinal injury, and bacterial translocation.15,16 Previously, a group including one of the authors (S.M.) also documented that nonlethal doses of endotoxin administered intraperitoneally promote bacterial translocation in a dose-dependent fashion.8

However, in intestinal I/R models, early theories of a bacterial pathogenesis have been replaced by the current scheme of an inflammatory process mediated by activated neutrophils and resulting in capillary dysfunction and macromolecular leakage.3 This experiment also shows that the AG challenge did not suppress either gut bacterial transloca-

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Table 1  Incidence and Magnitude of Bacterial Translocation (BT) to MLNs and Cecal Bacterial Population Level After Gut Ischemia-Reperfusion With or Without Aminoguanidine

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>BT to MLN Incidence*</th>
<th>Magnitude†</th>
<th>Cecal Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>6.1 ± 0.9</td>
</tr>
<tr>
<td>I/R</td>
<td>6</td>
<td>83</td>
<td>2.5 ± 0.9</td>
<td>7.0 ± 1.5</td>
</tr>
<tr>
<td>AG</td>
<td>6</td>
<td>50</td>
<td>1.9 ± 1.5</td>
<td>6.8 ± 0.6</td>
</tr>
</tbody>
</table>

* Incidence expressed as a percentage of culture-positive MLNs. † Magnitude of BT to MLN and bacterial cecal population levels expressed as means ± sd (log10 CFU/g tissue, gram-negative enterics).

Table 2  Concentration of Nitrite and Nitrate in Lungs and Plasma After Gut Ischemia-Reperfusion

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Lungs (mmol/g)</th>
<th>Plasma (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>9.15 ± 3.09</td>
<td>42.6 ± 22.5</td>
</tr>
<tr>
<td>I/R</td>
<td>6</td>
<td>19.5 ± 7.33*</td>
<td>491 ± 163*</td>
</tr>
<tr>
<td>AG</td>
<td>6</td>
<td>12.1 ± 6.83</td>
<td>273 ± 140‡</td>
</tr>
</tbody>
</table>

Data expressed as mean ± sd of nitrite and nitrate. * p < 0.05 versus control, † p < 0.05 versus I/R.

Table 3  Lung-to-Plasma (LP) Ratio of Evans Blue Dye Concentration After Gut Ischemia-Reperfusion

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>LP ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>6.64 ± 2.57</td>
</tr>
<tr>
<td>I/R</td>
<td>6</td>
<td>18.1 ± 3.70*</td>
</tr>
<tr>
<td>AG</td>
<td>6</td>
<td>11.0 ± 3.95</td>
</tr>
</tbody>
</table>

Data expressed as mean ± sd of LP ratio of EBD. * p < 0.05 versus control and AG.

Table 4  Incidence of Ileal Mucosal Damage After Gut Ischemia-Reperfusion

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Examined Villi</th>
<th>Incidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>120 ± 36</td>
<td>0</td>
</tr>
<tr>
<td>I/R</td>
<td>6</td>
<td>103 ± 24</td>
<td>35 ± 15†</td>
</tr>
<tr>
<td>AG</td>
<td>6</td>
<td>115 ± 41</td>
<td>25 ± 21†</td>
</tr>
</tbody>
</table>

* Incidence expressed as mean ± sd (%) of injured villi. † p < 0.01 versus control.

Fig. 1. Light microscopy appearance of the ileum. (A) Control has normal findings. Both (B) I/R and (C) AG tissues show decreased heights of villi in the injured mucosa.
tion or the histologic derangement of the ileum after the insult, but prevented pulmonary edema in the AG group. Currently, Deitch and his colleagues suggest that mesenteric lymph induced remote organ dysfunction in their trauma and shock model; therefore, gut bacterial translocation may not be a source of organ failure, but may actually be an indicator of mucosal barrier dysfunction and be related with systemic inflammatory process at second hand.

In this study, administered AG did not prevent gut mucosal injury after SMA occlusion. Studies of intestinal I/R suggested the existence of alternative systems that harm the mucosal barrier function. One proposed mechanism involves reactive oxygen species, especially those derived from xanthine and xanthine oxidase in the gut mucosa; thus, oxygen radical scavengers may improve the gut injury in this model. We documented that the utilization of the novel synthesized radical scavenger edaravone could prevent an endothelial monolayer injury induced by xanthine and xanthine oxidase in vitro. The combination of reactive oxygen species scavenger and AG may therefore ameliorate the intestinal barrier dysfunction, but this remains to be proven in a further study.

There are conflicting data supporting both a beneficial and a harmful effect of NO on acute lung injury induced by shock, endotoxiaemia, and I/R. Currently, most investigators think that the protective and detrimental effects of NO seem largely to reflect a dose-related phenomenon. Therefore, a group including one of the authors (S.M.) previously investigated the relationships among NO production, mucosal injury, and bacterial translocation in rats challenged with a non-lethal dose of endotoxin. One major finding of the study was that the dose of the competitive NOS inhibitor N\textsuperscript{G}-monomethyl-L-arginine, which improved gut injury, suppressed not fully constitutive NOS (cNOS) but iNOS activities in the MLNs, liver, and ileal tissue. These data are consistent with a current study indicating that relatively selective iNOS inhibitor AG reduced gut I/R-induced lung injury.

Low levels of NO production by the cNOS may protect an organ in the early stages of injury, whereas elevated and prolonged NO production by iNOS during the later stages of the insult may result in or potentiate organ injury. Therefore, we challenged the AG group with AG at the end of SMA occlusion and this suppressed NO production after the reperfusion period. The concentration of nitrite and nitrate in the plasma was more decreased in the AG group than in the I/R group.

The gut is a weak microcirculatory unit, and I/R injury of the gut is a clinically common pathologic situation. Remote vital organs, such as the lungs, are mainly injured after splanchic hypoperfusion including excessive NO production. Selective iNOS inhibitors could prevent acute lung injury in the SMA occlusion model by decreasing the prolonged and large amount of NO production. The dose response and time course of NO production seem important in the regulation of NO-induced organ injury.

ACKNOWLEDGMENTS

We thank Prof. J. Patrick Barron of the International Medical Communications Center of Tokyo Medical University for his review of this article.

REFERENCES


Pediatric Blunt Abdominal Injury: Age is Irrelevant and Delayed Operation is Not Detrimental

Monika Tataria, MD, Michael L. Nance, MD, James H. Holmes IV, MD, Charles C. Miller III, PhD, Kelly D. Mattix, MD, Rebecca L. Brown, MD, David P. Mooney, MD, L. R. Tres Scherer III, MD, Jon I. Groner, MD, Eric R. Scaife, MD, David A. Spain, MD, and Susan I. Brundage, MD

Background: During the past 40 years, management of solid organ injury in pediatric trauma patients has shifted to highly successful nonoperative management. Our purpose was to characterize children requiring operative intervention. We hypothesized that older children would be more likely to require operative intervention. In particular, we wanted to examine potential outcome disparities between children who were operated upon immediately and those in whom attempted nonoperative management failed. Additionally, we asked whether attempted nonoperative management, when failed, put children at higher risk for mortality or morbidities such as increased blood product transfusions or lengths of stay.

Methods: Retrospective cohorts from seven Level I pediatric trauma centers were identified. Blunt splenic, hepatic, renal, or pancreatic injuries were documented in 2,944 children <1 to 19 years of age from January 1993 to December 2002. Data collected included demographics, hemodynamics, blood transfusions, Glasgow Coma Scale score, Injury Severity Score, hospital length of stay (LOS), intensive care unit (ICU) LOS, and mortality. Analysis involved 140 patients (<3 hours after arrival (n = 81; 58%) and (2) failed nonoperative management (F-NOM), defined as laparotomy >3 hours after arrival (n = 59; 42%).

Results: Comparing the two cohorts, no age differences were found. Compared with F-NOM, IO had significantly worse hemodynamics, Injury Severity Score, and Glasgow Coma Scale score and was associated with liver injuries. Pancreatic injuries were significantly associated with F-NOM. While controlling for injury severity to compare IO versus F-NOM, linear regression revealed equivalent blood transfusions, ICU LOS, hospital LOS, and mortality rates.

Conclusion: IO and F-NOM are rare events and independent of age. When operated upon for appropriate physiology, the timing of operation in pediatric solid organ injury is irrelevant and not detrimental with respect to blood transfusion, mortality, ICU and hospital LOS, and resource utilization.

Key Words: Pediatric trauma, Blunt abdominal trauma, Solid organ injury, Nonoperative management, Liver, Kidney, Spleen, Pancreas.

Histologically, solid organ injury resulting from blunt abdominal trauma was treated with immediate operative intervention. In recent decades, treatment of solid organ injury has shifted to nonoperative management. This shift began with observational management of splenic injuries in the pediatric population described 40 years ago¹ and has slowly become the standard of care for management of blunt injuries to the spleen, liver, kidney, and pancreas in adults as well as children.

On the basis of the results of numerous studies examining solid organ injury, it is clear that, in children sustaining blunt abdominal trauma, the majority of hemodynamically stable patients should undergo nonoperative management with a >90% success rate.²⁻⁹ Only a small percentage of all patients injured will require laparotomy or have complications as a result of the nonoperative management. The purpose of this multicenter study was to characterize the cohort of patients that require operative intervention as a result of solid organ injury from blunt abdominal trauma. We hypothesized that older children would be more likely to require operative intervention because previous studies regarding nonoperative management for splenic trauma have shown that older children and adults have higher rates of operation.¹⁰⁻¹² Additionally, we sought to compare children who underwent immediate operation (IO) with children in whom nonoperative management was initially attempted but failed to determine whether there were any differences in outcomes. We questioned whether attempted nonoperative management, when failed, puts children at higher risk for mortality or...
morbidities such as increased blood product transfusions or lengths of stays.

**PATIENTS AND METHODS**

The trauma registries of seven Level I pediatric trauma centers were reviewed to identify all children less than 19 years of age sustaining blunt trauma to the spleen, kidney, liver, and pancreas during the 10-year period from January 1993 to December 2002. Institutional review board’s approval was obtained from all participating institutions. Data reviewed included age, gender, injury mechanism, Injury Severity Score (ISS), Glasgow Coma Scale (GCS) score, grade of organ injury, and mortality. Of the patients identified, additional data were collected on patients who required operative intervention. These data included hospital length of stay (LOS), intensive care unit (ICU) LOS, systolic blood pressure, heart rate on arrival and before going to the operating room, transfusion requirements, and time elapsed before operation. Two cohorts were identified among the patients who required operative intervention based on the amount of time that elapsed before going to the operating room. Patients who underwent IO were those who underwent laparotomy <3 hours after arrival to the emergency room (ER). Patients who had failed nonoperative management (F-NOM) were those who underwent laparotomy >3 hours after arrival to the ER. Three hours was chosen to distinguish IO and F-NOM to allow for radiographic work-up and ER resuscitation. Linear regression analysis for outcome was performed on these two cohorts controlling for ISS, GCS score, age, and grade of organ injury. Outcomes measured were mortality, blood transfusion requirements, hospital LOS, and ICU LOS.

**RESULTS**

We identified 2,944 children who sustained blunt abdominal injury during the study period. Of these patients, there were a total of 2,981 organ injuries because some patients sustained multiple organ injuries. Of the 2,981 organs injured, 46.7% (n = 1,392) were splenic injuries, 33.3% (n = 994) were liver injuries, 17.5% (n = 520) were renal injuries, and 2.5% (n = 75) were pancreatic injuries (Fig. 1).

The overall rate of operation was low, as expected. Only 140 of the 2,944 patients required laparotomy (4.8%). Characteristics of the patients requiring laparotomy were compared with those of the control patients, who did not require operation (Table 1). The mean age of control patients (8.9 years) was not significantly different from the mean age of patients requiring operation (9.1 years). In both groups, male patients were predominant (68.8% of controls vs. 64% of patients requiring operation). The patients requiring operation were more severely injured than were the control patients. This was indicated by a significantly higher mean ISS in children requiring operation (28.7) compared with in controls (14.6; p < 0.001), and a significantly lower median GCS score (12 for patients requiring operation vs. 14 for controls; p < 0.001; Table 1). Rates of operation were statistically similar for patients who sustained injury to the spleen (4.8%), liver (5.8%), and kidney (6.1%). Children requiring laparotomy were significantly more likely to have sustained injury to the pancreas than were control patients (p < 0.05). When broken down by age group, there was no difference in the age

![Abdominal Organ Injured In All Children Sustaining Blunt Abdominal Trauma](image)

**Fig. 1. Abdominal organ injury in all children sustaining blunt trauma.**

<table>
<thead>
<tr>
<th>Table 1 Characteristics of Children Sustaining Blunt Abdominal Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong> (n = 2,804 Patients)</td>
</tr>
<tr>
<td>Mean age, yr (mean ± SD)</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>Mean ISS (mean ± SD)</td>
</tr>
<tr>
<td>Median GCS score</td>
</tr>
<tr>
<td>Organ injured (% of cohort)†</td>
</tr>
<tr>
<td>Liver, n (%)</td>
</tr>
<tr>
<td>Spleen, n (%)</td>
</tr>
<tr>
<td>Pancreas, n (%)</td>
</tr>
<tr>
<td>Kidney, n (%)</td>
</tr>
</tbody>
</table>

† Total number of organs injured = 2,981.
NS, not significant.
of children requiring laparotomy for blunt abdominal trauma. Younger children were as likely to require exploration as older children were; ages: 0 to 4 (27 of 604; 4.5%), 5 to 9 (43 of 953; 4.5%), 10 to 14 (59 of 1,027; 5.7%), 15 to 19 (11 of 360; 3.1%) (Fig. 2).

Next, we separated the 140 patients who required operation into two cohorts on the basis of the time elapsed before laparotomy. Eighty-one patients (58%) required IO (operation within 3 hours of arrival to the ER). Fifty-nine patients (42%) underwent attempted nonoperative management, which failed, thus requiring laparotomy greater than 3 hours after presentation. Demographically, patients who underwent IO and those who had F-NOM were similar. Children who underwent IO had mean age of 8.6 years and 63.2% were male. Those who had F-NOM had a mean age of 9.7 years and 68% were male. Children requiring IO had significantly worse ISSs (p < 0.001) and GCS scores (p < 0.001) than patients who had F-NOM. They also had significantly lower systolic blood pressure and higher heart rates than those patients who had F-NOM (Table 2). In children requiring operation, age was not related to whether patients required IO or whether they had F-NOM (Fig. 3). The most common reason that both groups of patients that required operative intervention was hemodynamic instability or bleeding (n = 77, 55%). Other reasons included peritonitis and pancreatic transaction or avulsion (Table 3). Patients with pancreatic injuries were significantly more likely to require delayed operation, whereas patients with liver injury were significantly more likely to require IO. Linear regression analysis controlling for ISS, GCS score, demographics, and severity of organ injury showed that children who had F-NOM have similar ICU lengths of stay, hospital lengths of stay, transfusion requirements, and mortality rates as those who underwent IO (Table 4).

DISCUSSION

In the pediatric population, the spleen is the most commonly injured organ. In 1951, King and Schumacher found that children have increased susceptibility to infection after splenectomy. In the late 1960s, to prevent overwhelming postsplenectomy infection, a few surgeons began to manage selected patients nonoperatively. Upadhyaya and Simpson pioneered selective nonoperative management of children with splenic injuries from blunt abdominal trauma. Subsequently, pediatric surgeons began to shift their manage-

![Fig. 2. Percent of children with solid organ injury requiring operative intervention. Older children were not more likely to require operative intervention.](image)

![Fig. 3. Breakdown of children requiring operative intervention by age. Younger children had similar rates of F-NOM as older children.](image)

### Table 2 Characteristics of Children Requiring Operation

<table>
<thead>
<tr>
<th></th>
<th>Immediate Operation (n = 81)</th>
<th>Failure of Nonoperative Management (n = 59)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr (mean ± SD)</td>
<td>8.6 ± 4.3</td>
<td>9.7 ± 4.1</td>
<td>0.15</td>
</tr>
<tr>
<td>Male (%)</td>
<td>63.2</td>
<td>68</td>
<td>NS</td>
</tr>
<tr>
<td>Mean ISS (mean ± SD)</td>
<td>33.2 ± 18.1</td>
<td>22.4 ± 14</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median GCS score</td>
<td>10</td>
<td>14</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Preoperative systolic blood pressure (mean ± SD)</td>
<td>104.8 ± 22.8</td>
<td>115.0 ± 17.7</td>
<td>0.007*</td>
</tr>
<tr>
<td>Preoperative heart rate (mean ± SD)</td>
<td>124.7 ± 30</td>
<td>114.0 ± 28</td>
<td>0.04*</td>
</tr>
<tr>
<td>Liver, n (%)</td>
<td>44 (54.3)</td>
<td>15 (25.4)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Spleen, n (%)</td>
<td>44 (54.3)</td>
<td>26 (44.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Pancreas, n (%)</td>
<td>17 (21)</td>
<td>26 (44.1)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Kidney, n (%)</td>
<td>21 (25.9)</td>
<td>12 (20.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* p < 0.05.
NS, not significant.
ment from immediate laparotomy for all patients to selective nonoperative management. Wesson et al. described one of the first algorithms for nonoperative management of the injured spleen in children in the 1980s, with the decision matrix guided by physical examination and monitoring of vital signs. Facilitated by the use of computerized tomography during the 1990s, nonoperative management of blunt splenic injuries became the most common method of management. Pediatric patients have an anticipated success rate of greater than 90% with nonoperative management. 10,11,19

In adults, only 65% of patients are reported as being successful in managing splenic injuries. The odds ratio for risk of splenic operation increased 4.4-fold when a child was treated in a Level I trauma with additional pediatric qualifications. There was a 6.3-fold increase in splenectomy for Level I trauma centers, and a 5.0-fold increase in nontrauma hospitals. Davis et al.’s study shows that management of splenic injury varies greatly according to hospital trauma status, and encourages standardization and widespread adoption of nonoperative techniques, given the potential benefits of nonoperative management.

Recently, Davis et al. used statewide hospital discharge data from Pennsylvania, which has a well-developed regional trauma system to assess trends in operative management from splenic injury. During a 10-year period from 1991 to 2000, they found a 23.2% operative rate for splenic trauma in 3,245 patients. All patients met the inclusion criteria of <19 years of age. Compared with treatment in a specific pediatric trauma center, the relative risk of having a splenectomy increased 1.5-fold for children treated in a Level I trauma center, the relative risk of having a splenectomy increased 4.4-fold when a child was treated in a Level I trauma with additional pediatric qualifications. There was a 6.3-fold increase in splenectomy for Level I trauma centers, and a 5.0-fold increase in nontrauma hospitals. Davis et al.’s study shows that management of splenic injury varies greatly according to hospital trauma status, and encourages standardization and widespread adoption of nonoperative techniques, given the potential benefits of nonoperative management.

<table>
<thead>
<tr>
<th>Table 3 Reasons for Operative Intervention</th>
<th>Number (%) of Children (N = 1499)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding (hemodynamic instability, decreased hematocrit, ongoing transfusion requirements)</td>
<td>77 (55)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Vascular injury</td>
<td>5 (3.6)</td>
</tr>
<tr>
<td>Free air</td>
<td>9 (6.4)</td>
</tr>
<tr>
<td>Pancreatic transaction or avulsion</td>
<td>16 (11.4)</td>
</tr>
<tr>
<td>Abdominal compartment syndrome</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Possible infection</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Pancreatic pseudocyst</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Suspected bowel injury</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (5.7)</td>
</tr>
</tbody>
</table>

| Table 4 Outcomes of Children Sustaining Blunt Abdominal Trauma as Determined by Linear Regression Analysis |
|---------------------------------------------------------------|-------------------|---------------------------------------------------------------|-------------------|
| Immediate Operation (n = 81) | Failed Nonoperative Management (n = 59) | p (Odds Ratio; 95% CI) |
|-----------------------------|-------------------|---------------------------------------------------------------|-------------------|
| ICU LOS (days) | 4.3 | 3.2 | 0.27 |
| Length of stay (days) | 10.3 | 13.4 | 0.15 |
| Transfusions (mL) | 330.2 | 442.3 | 0.18 |
| Mortality (adjusted ISS and GCS sore) (%) | 25/81 (30) | 6/59 (6.8) | 0.15 (3.14; 0.66–14.9) |
Again, the authors call for increased surgeon education and dissemination of the American Pediatric Surgical Association guidelines and benchmarks throughout trauma systems in an effort to save spleens.

Both Jacobs et al. and Myers et al. have shown that dedicated trauma surgeons can achieve high rates of successful nonoperative management in patients of all ages. Our data adds to the literature that supports that it is not the age of the patient that is associated with increased rates of splenectomy, rather that the increased rates of splenectomy, as seen in the previous studies, are most likely a reflection of the treating center and or treating surgeon.

Because the spleen is the most studied solid organ to be managed nonoperatively, trauma surgeons have applied the principles learned from successful nonoperative management of the spleen to other solid abdominal organs. Although the majority of solid organ injuries may be managed nonoperatively, the anatomy and physiology of the spleen, liver, kidney, and pancreas are very different. Therefore, the sequela of injuries to these organs varies. The data from this study are suggestive of these differences in that patients with liver injury are least likely to fail nonoperative management, whereas children with pancreatic injuries most likely require delayed operation.

The liver is the second most commonly injured organ in children sustaining blunt abdominal trauma. In 1983, pediatric surgeons showed that blunt hepatic trauma could also be successfully managed nonoperatively. During the 1990s, trauma surgeons began to apply nonoperative management of liver injuries to their adult patients. In 1996, Bond showed that approximately 97% of children with liver injuries from blunt abdominal trauma could be treated nonoperatively without complications. Similarly, it has been shown that more than 90% of adults with liver injuries may be managed nonoperatively.

Renal trauma secondary to blunt abdominal injury is relatively rare. Children are more susceptible to renal trauma secondary to anatomic differences (less perirenal fat and weaker muscles). The majority of renal trauma is minor with 90% of all injuries categorized as grades I and II. This observation along with finding that operative management led to higher rates of nephrectomy led to a shift in the nonoperative management of blunt renal trauma. In 2004, a retrospective study showed that nonoperative management of renal trauma is successful in 95% of children with renal injury from blunt abdominal trauma.

Pancreatic injuries are also relatively infrequent in children. Pancreatic injuries have been managed nonoperatively in adults for many years. More recently, surgeons have started to apply nonoperative management to pancreatic injuries in children. Pancreatic injuries in our study were significantly more likely to require operative intervention compared with splenic, liver, and renal injuries. Pancreatic injury for the F-NOM group was diagnosed by CT scan or during laparotomy performed for peritonitis or bleeding. Although these relationships do not give us enough information to optimize management based on the specific organ injured, they do suggest that management guidelines should be organ specific.

We also attempted to elucidate whether nonoperative management, when failed, puts children at higher risk for mortality or morbidities such as increased blood product transfusions or lengths of stays. Previous works have shown that nonoperative management of solid organ injuries results in decreased blood utilization. Blood product administration is clearly associated with an increase in infectious complications and mortality in multiple studies. The majority of studies examining the blood transfusion requirements in nonoperative management have compared the two cohorts of successful nonoperative management versus laparotomy. Our goal was to compare the two cohorts of IO and F-NOM. We questioned whether F-NOM resulted in increased blood requirements. Our analysis has shown that there are no adverse outcomes to children in terms of mortality, blood transfusion requirements, or hospital and ICU LOS if nonoperative management was initially attempted, but failed.

Limitations of the Current Study

The retrospective nature of this study means that it has certain inherent flaws. Because the data were gathered from trauma databases and patient charts during a 10-year period, detailed information was not available regarding the surgeon's decision-making process regarding which patients required IO versus which could undergo nonoperative management. Our decision to use 3 hours as the differentiation point between IO and F-NOM is also arbitrary and can be criticized.

As reported in Results, younger children were as likely to require exploration as older children; ages: 0 to 4 (27 of 604; 4.5%), 5 to 9 (43 of 953; 4.5%), 10 to 14 (59 of 1,027; 5.7%), 15 to 19 (11 of 360; 3.1%). These differences were not statistically significant. Granted, there could be a type II statistical error because only three patients underwent IO compared with eight patients who had F-NOM in the 15 to 19 age group.

The accuracy of the information gathered in a retrospective study is limited and it is sometimes incomplete. For example, in this study, we could not comment on complications of nonoperative management because these data were missing from many of the patients. Additionally, information regarding organ-specific complications would help design guidelines for management of the patients. It would be valuable if we could comment on any differences in trends regarding the selection of management during the 10-year period. Unfortunately, with the current data set we cannot answer the question regarding changes in management over time because admission dates were not included in the data collected. Admittedly, this is a fault in the study design and conception of the database. A prospective study could potentially provide more detailed information regarding dif-
ferences between the two cohorts, allowing surgeons to determine practice guidelines that could be used to determine which patient should undergo IO, what timeline actually constitutes IO, and which patients can be safely managed nonoperatively.

CONCLUSIONS
This multicenter study confirms that nonoperative management is successful in >95% of patients. Older children are not more likely to require operative intervention for solid organ injury as a result of abdominal trauma. Regarding the question of age, as more data are accumulated, it appears that the increased rates of splenectomy in older children may not be dictated by physiologic need but by the practice standards and culture of the treating institutions as well as the experience and comfort level of the treating surgeons. Rates of operative intervention in children sustaining injuries to the spleen (4.8%), liver (5.8%), and kidneys (6.1%) are statistically similar. However, children with pancreatic injuries are much more likely than children with other solid organ injuries to require operative management (57% of pancreatic injuries required surgical intervention) and are also more likely to fail trials of nonoperative management. Children with hepatic injuries, on the other hand, are more likely to require IO if they are going to need operative intervention. Children who fail a trial of nonoperative management do not have adverse outcomes in terms of mortality, ICU LOS, hospital LOS, or blood transfusion requirements.

REFERENCES
Experience With Splenic Main Coil Embolization and Significance of New or Persistent Pseudoaneurysm: Reembolize, Operate, or Observe

James M. Haan, MD, Helen Marmery, MBChB, FRCR, Kathirkamanathan Shanmuganathan, MD, Stuart E. Mirvis, MD, and Thomas M. Scalea, MD

**Background:** To determine the need for further therapy in patients with persistent or new pseudoaneurysms (PSAs) after splenic main coil embolization.

**Methods:** The institutional review board approved the study. The study group consisted of 400 hemodynamically stable patients (261 men, 139 women; mean age, 38.5 years) with blunt splenic injury. Abdominal computed tomography (ACT) images were assessed for grade of splenic injury, volume of hemoperitoneum, and evidence of splenic vascular injury including splenic vascular lesions and active bleeding. Splenic arteriography was performed for high-grade splenic injury and for ACT evidence of vascular injury. Follow-up ACT was reviewed for evidence of new or persistent PSAs after main coil embolization of the splenic artery. Medical records were reviewed to determine final outcome and any additional therapies used.

**Results:** Thirty-two patients had persistent (27) or new PSAs (5) after main coil embolization. Of these patients, two required splenectomy and one splenorrhaphy. The nonoperative salvage rate was 91%, and the splenic salvage rate was 94%; this was comparable to the overall salvage rate of 95%.

**Conclusion:** Splenic embolization remains a valuable adjunct in splenic salvage. Patients with persistent or new splenic PSAs after main coil embolization have similar splenic salvage rates to the overall cohort without additional therapies.

**Key Words:** Pseudoaneurysm, Angiography, Nonoperative management, Splenic injury, Embolization.


No operative management of splenic injury has become the standard of care in hemodynamically stable adult patients with blunt splenic injury. Some trauma centers, including our own, use splenic arteriography and embolization of vascular injuries as an adjunct to improve the success rate of nonoperatively managed splenic injuries. We began using splenic embolization in 1997 to enhance splenic salvage rates. Based on our early experience, we have abandoned the use of super selective embolization in favor of main coil splenic embolization. We found main coil embolization to be faster, less expensive, technically easier, and that it demonstrated a trend toward improved splenic salvage. With this transition we have also noted a new entity: patients with persistent or new splenic pseudoaneurysms after main coil embolization. This left the question: what is the risk of nonoperative failure in this subgroup and does it warrant further angiographic or operative therapies. A prospective study was performed to determine the incidence of persistent and new splenic artery pseudoaneurysms after main coil embolization and the incidence of nonoperative failure in this group.

**PATIENTS AND METHODS**

**Patients**

The institutional review board approved the study as a surgical and radiographic collaboration. Written informed consent was obtained from 76 patients. The institutional review board subsequently waived informed consent for the subsequent 324 patients.

**Splenic Arteriography**

Splenic arteriography was performed on all hemodynamically stable patients with high-grade splenic injury (American Association for the Surgery of Trauma Organ Injury Score grades 3–5) and low-grade splenic injury (grades 1 and 2) who demonstrated active bleeding or vascular lesions on abdominal computed tomography (ACT). Proximal main splenic artery embolization was performed if there was evidence of pseudoaneurysm (PSA), arteriovenous fistulae (AVF), or active bleeding confined to the spleen. Selective coaxial microcoil distal splenic artery branch embolization was performed in addition to main splenic artery embolization if active contrast extravasation into the peritoneal cavity was noted. Proximal main splenic artery embolization was performed for angiographic evidence of active extravasation, AVF, PSA, or secondary evidence of vessel injury defined by
operative management was defined as the patient with follow-up CT and outpatient record review. Success of non-performed, the outcome measure was clinical and based on coil embolization. When neither angiography nor surgery was interest: those patients undergoing main coil embolization outcome and in the overall population and the subset of assessed mechanism of injury, Injury Severity Score (ISS), and ports (if applicable), and outpatient records were reviewed to fied from the method described by Federle et al., including the perisplenic space, Morison’s pouch, left and right paracolic gutters, and pelvis. “Small” hemoperitoneum was defined as blood seen in only one or two anatomic areas on axial multidetector-row CT (MDCT) images, “moderate” as blood seen in three or four areas, and “large” as blood in all five locations.

Two of the authors (K.S., S.M.) retrospectively compared prospectively collected ACT reports with splenic arteriographic images and final interpretations to determine whether active bleeding or vascular lesions were detected on the initial MDCT interpretation. Two interventional radiologists without knowledge of the CT interpretation reevaluated splenic arteriography images for all MDCT and splenic arteriographic cases with discrepant reports. Their consensus opinion was used as the final splenic arteriogram report. Two radiologists with knowledge of the final splenic arteriogram interpretation retrospectively reviewed CT images of all discrepant cases to determine whether active bleeding or splenic vascular lesions were present or missed on initial interpretation.

Definitions and Image Analysis

Initial ACT images were prospectively and independently reviewed by a senior resident, and by four board-certified emergency radiologists with 3 to 20 years experience. Splenic injury was graded according to the American Association for the Surgery of Trauma Organ Injury Score splenic injury scale. When the initial computed tomography (CT) images were reported as normal but the patient was subsequently diagnosed as having a splenic injury based on follow-up CT or surgery, a splenic injury grade of 0 was retrospectively assessed.

Both active bleeding and splenic vascular lesions were considered as “vascular injuries” for this study. The presence of active bleeding or vascular lesion, including PSAs and traumatic AVF, was documented. The quantity of hemoperitoneum was documented as small, moderate, or large. The peritoneum was divided into five anatomic locations, modified from the method described by Federle et al., including the perisplenic space, Morison’s pouch, left and right paracolic gutters, and pelvis. “Small” hemoperitoneum was defined as blood seen in only one or two anatomic areas on axial multidetector-row CT (MDCT) images, “moderate” as blood seen in three or four areas, and “large” as blood in all five locations.

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Clinical Review and Statistical Analysis

The results of all follow-up ACT scans, laparotomy reports (if applicable), and outpatient records were reviewed to assess mechanism of injury, Injury Severity Score (ISS), and outcome and in the overall population and the subset of interest: those patients undergoing main coil embolization with persistent or new splenic PSAs after splenic artery main coil embolization. When neither angiography nor surgery was performed, the outcome measure was clinical and based on follow-up CT and outpatient record review. Success of non-operative management was defined as the patient with the spleen in situ and with no need for splenic surgery at last clinical follow-up.

RESULTS

Between October 2002 and May 2005, 496 patients aged 18 years or older were admitted to our institution with blunt splenic trauma. Patients who underwent angiography (n = 5), laparotomy (n = 8), or splenectomy (n = 32) before ACT imaging were excluded. An additional 51 patients were excluded because of death within 24 hours (n = 10), inadequate follow-up (n = 17), presentation from an outside hospital (n = 4), delayed CT (n = 2), iatrogenic splenic injury (n = 1), unavailable imaging (n = 7), technically inadequate CT (n = 9), and incomplete clinical information (n = 1). A total of 400 patients (261 men, 139 women; age range, 18–86 years; mean age, 38.5 years) formed the study group.

Mechanisms of injury for the 400 study patients and those patients with persistent or new PSAs after splenic main coil embolization (PSA group) were predominantly motor vehicle collisions as detailed in Table 1. These were statistically similar to the overall cohort. Table 2 lists the results of splenic injury grades for the overall group and the number of vascular injuries identified in each grade. Hemoperitoneum was quantified as none in 115 patients (29%), small in 110 patients (27.5%), moderate in 83 patients (21%), and large in 92 patients (23%). A positive association was found between the volume of hemoperitoneum and presence of a vascular injury (γ = 0.49; SD = 0.07; p < 0.0001). The mean ISS of the study group was 26 (range, 1–75).

| Table 1 Mechanism of Injury for Total Group and PSA |
| Group | Total Study (PTS) | PSA |
| MVC | 279 | 21 |
| Fall | 43 | 5 |
| MCC | 33 | 0 |
| Assault | 10 | 3 |
| Ped struck | 22 | 1 |
| Bicycle | 3 | 0 |
| Other | 10 | 2 |
| MVC, motor vehicle collision; MCC, motorcycle collision; Ped struck, pedestrian struck by vehicle; PTS, patients; PSA, pseudoaneurysm. |

| Table 2 Total Group Splenic Injury Grade and Vascular Injury at Admission ACT |
| Grade of Injury | PTS | No. Patients With Vascular Injuries | Percent With Vascular Injury |
| | Total | Active Bleeding | Pseudo Aneurysm | |
| 0 | 8 | 0 | 0 | 0 |
| 1 | 102 | 4 | 2 | 3 |
| 2 | 111 | 16 | 2 | 14 |
| 3 | 114 | 33 | 10 | 28 |
| 4 | 49 | 21 | 16 | 10 |
| 5 | 16 | 12 | 10 | 5 |
| PTS, patients; ACT, abdominal computed tomography. |
Table 3 PSA Group Splenic Injury and Vascular Injury at Admission ACT

<table>
<thead>
<tr>
<th>Grade of Injury</th>
<th>PTS Total (Failures)</th>
<th>No. Patients With Vascular Injuries</th>
<th>Percent With Vascular Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Active Bleeding</td>
<td>Pseudoaneurysm</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
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<tr>
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</tr>
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</table>

PTS, patients; PSA, pseudoaneurysm; ACT, abdominal computed tomography; failures, failures in nonoperative management.

Table 3 demonstrates the incidence of splenic injury grades for the PSA group and the number of vascular injuries identified in each grade. This incidence is higher than the overall cohort, 27 of 32 patients, but this to be expected because, by definition, 27 underwent main coil embolization for vascular injury with five patients undergoing delayed embolized for new PSAs. Hemoperitoneum in the PSA group was quantified as none in five patients (15%), small in eight patients (25%), moderate in six patients (21%), and large in 92 patients (23%). The higher quantity of hemoperitoneum is also to be expected with the higher splenic injury grade (2.35 overall vs. 3.0 PSA) and incidence of vascular injury (22% vs. 84%).

Vascular Injuries

Splenic vascular injury, including vascular lesion or active bleeding, was seen in 22% of patients (86 of 400) on initial CT. Vascular lesions were seen in 46 patients (25 single, 21 multiple), 26 patients had active bleeding, and 14 patients demonstrated both of these findings (Table 2). The presence of a vascular injury correlated significantly with the severity of the injury grade ($\gamma = 0.64$; SD = 0.059; $p < 0.0001$).

Of 40 patients with active bleeding on initial CT, 21 (52%) required splenectomy immediately after CT. Only four of 46 patients (9%) with PSA required immediate splenectomy. The presence of splenic active bleeding on MDCT highly correlated with splenectomy when compared with the presence of PSA ($p < 0.0001$).

Of 19 patients with active bleeding who were managed nonoperatively, 18 were treated successfully with splenic artery embolization without need for splenic surgery. Splenectomy was required in one patient for postembolization splenic hemorrhage. Splenic artery embolization successfully controlled bleeding in 95% (18 of 19) of patients.

Forty-five patients required immediate laparotomy and splenectomy after CT based on clinical parameters in combination with MDCT findings. The attending trauma surgeon made this decision. The mean ISS for this group was 34.5. The ISS for the surgery group was significantly higher than for the nonoperative treatment group (34.5 and 24.8, respectively; $p < 0.001$). In 13 cases, splenectomy was performed for reasons other than uncontrolled hemorrhage including significant injury to organs adjacent to the spleen (pancreas, n = 2; left hemidiaphragm, n = 2; and left kidney, n = 1), anticoagulation required for a vertebral artery injury (n = 2), persistent intraoperative hypotension (n = 4), high-grade splenic injury in a pregnant patient (n = 1), and onset of splenic bleeding when the spleen was mobilized at surgery (n = 1). A total of five patients were found to have either a splenic injury that was not detected on ACT (n = 3) or active bleeding from the spleen at laparotomy that was not demonstrated on abdominal MDCT (n = 2). The reason for splenectomy could not be determined from the surgical records of two patients.

Nonoperative management was attempted in 89% (355 of 400) of patients with blunt splenic injury. The mean ISS for this group was 24.8. Within this group, 340 patients (95%) were successfully managed without splenic surgery. The overall splenic salvage rate for blunt splenic injury was 85% (341 of 400). The success rate of nonoperative management had a significant inverse association with grade of splenic injury ($\gamma = -0.54$; SD = 0.15; $p < 0.0002$) (Table 2). For high-grade injuries (grade 3–5), the success rate of nonoperative management was 95% (136 of 143) with an overall splenic salvage rate of 76%. The failure rate of nonoperative management was 5% (15 of 355), and 14 patients required splenectomy and one required splenorrhaphy.

Splenic Arteriography

Splenic arteriography was performed in 164 patients (mean ISS, 25.5). A total of 130 splenic artery embolizations were performed, a therapeutic ratio of 78%. Nonoperative failure rate in the embolization group was 73% (9 of 130).

Persistent and New PSAs After Embolization

Of those embolized, 32 patients had pseudoaneurysms after splenic main coil embolization (27 persistent and 5 new pseudoaneurysms). Mechanisms of injury were similar to the overall cohort as stated prior and can be seen in Table 1. A higher incidence of vascular injury and quantity of hemoperitoneum was seen within this embolized group in comparison with the overall cohort.

There were three nonoperative failures within this subgroup; two patients required splenectomy and one splenorrhaphy. All failures were of higher splenic injury grade (given in parenthesis in Table 3). Failure was not related to associated injuries as all patients who failed had isolated splenic injuries (Table 4). All failures occurred during initial hospitalization. Two patients required operation on day 2 (one splenectomy and one splenorrhaphy) for decreasing hematocrits. The other patient failed on day 6 for increasing abdominal pain and rupture of subcapsular hematoma. All were hemodynamically stable and suffered no postoperative complications.
Ablation of therapy is a more widely used modality in nonoperative splenic salvage. This study demonstrates the utility of a protocol selectively using admission angiography. In the current study, the success rate of nonoperative management had a significant inverse correlation with splenic injury grade ($\gamma = -0.54$). A similar trend was reported by Peitzman et al. in a large, multi-institutional study performed to determine factors that predict successful management of splenic injury. Several studies have also attempted to demonstrate specific CT findings that help with therapeutic decisions and correlate with outcomes. 2,3,8–19

Despite the protocol, four patients were lost to follow-up after 2 weeks (1 patient had undergone splenectomy, 3 patients had had persistent splenic PSAs). Of the remainder, eight patients had 1-month follow-up and the rest were followed for 3 to 6 months with no clinical bleeding. Fourteen patients underwent reimaging during admission with resolution of six PSAs. One patient early in the experience, at 2 weeks, underwent follow-up angiography, which confirmed PSA resolution. An additional eight patients had outpatient scans at our or local institutions confirmed PSA resolution. Taking into account deaths, patients undergoing surgery, and stated follow-up ACT and angiographic examination, five patients were left who had been followed clinically (all greater than 3 months without bleed) and three patients who were lost before follow-up ACT.

**DISCUSSION**

Splenic embolization has become a more widely used adjunct in nonoperative splenic salvage. This study demonstrates the utility of a protocol selectively using admission angiography. In the current study, the success rate of nonoperative management had a significant inverse correlation with splenic injury grade ($\gamma = -0.54$). A similar trend was reported by Peitzman et al. in a large, multi-institutional study performed to determine factors that predict successful management of splenic injury. Several studies have also attempted to demonstrate specific CT findings that help with therapeutic decisions and correlate with outcomes. 2,3,8–19

These studies suggest that the presence of splenic vascular injury, including active bleeding and vascular lesions, correlate with a higher failure rate of nonsurgical management. The presence of a large hemoperitoneum has also been shown to be a predictor of failed nonoperative management. These predictors of vascular injury, quantity of hemoperitoneum, and increasing splenic injury grade remain true, but at far lower failure rates than prior studies. 1,7–13,15,17

This review also outlines one caution, a 52% failure rate in patients with active bleeding on ACT at admission. In those who were stabilized sufficiently for embolization, salvage rates remain high (95%) but a low threshold for operative therapy must remain in this subgroup as opposed to those with simple PSA that contained hemorrhage with a 9% total failure rate.

In patients with persistent or new PSAs after main coil embolizations, a 91% nonoperative success rate and a 94% splenic salvage rate were seen. These are statistically similar to rates in the embolized patient subgroup and overall cohort despite no additional therapies. The three patients requiring surgery failed early in the course, two from clinical bleeding and one from capsular rupture with complaint of pain. This patient with capsular rupture requiring surgery is of some concern as in our prior experience, nonoperative failures occurred by observation on day 3. 1,18,19 With the limited sample, it is not clear if additional observation is warranted by this single event or 3% incidence. With three other patients lost to follow-up the true incidence is unclear. We found the majority of PSAs resolved on follow-up imaging and did not affect clinical decision-making. We recommend for reliable patients discharge on hospital day 3 with precautions without further imaging or repeat angiography as the majority of the patients demonstrated resolution of the PSA on follow-up imaging and clinically did well. In those participating in high-risk behaviors or flight risk, additional observation with follow-up ACT is warranted to confirm PSA resolution as patient may not return for further outpatient follow-up.

It is important to note that this study was performed in a high-volume Level I trauma center with 24/7 in-house surgical coverage and operating room access. The results should not be extrapolated to smaller centers without rapid surgical evaluation and operating room availability. The risks of delayed bleeding without access to immediate therapy would outweigh the benefit of potential splenic salvage in higher-grade injury. Such centers must honestly assess their capabilities and consider earlier operative therapy or transfer to a center that has the surgical resources for safe nonoperative therapy.

**CONCLUSION**

Splenic embolization remains a valuable adjunct in splenic salvage. Patients with persistent or new splenic PSAs after main coil embolization have similar splenic salvage rates to the overall cohort without additional therapies. Patients with active bleeding into the peritoneum have a high risk of nonoperative failure and must be approached cautiously with a low threshold for conversion to operative treatment.
REFERENCES


Incidence of Early Pulmonary Embolism After Injury

Jay Menaker, MD, Deborah M. Stein, MD, MPH, and Thomas M. Scalea, MD

Background: Pulmonary embolism (PE) is a well-recognized potentially fatal complication after trauma. PE is generally thought to occur days after the acute injury. Hypoxia early after injury is often ascribed to other causes. We hypothesized that PE often occurs early after injury and we sought to elucidate the timing of PE after trauma.

Methods: The trauma registry was used to identify all patients diagnosed with an acute PE between June 1999 and December 2004. Medical records were reviewed and demographics, injury specific data, length of stay, comorbidities, and mortality were recorded. Time from injury to diagnosis was recorded as was diagnostic modality and treatment.

Results: In total, 35,424 patients were treated in our trauma center during the study period. Ninety-four patients with PE were identified (0.27%). Mean age was 45 (±18.5) years and mean Injury Severity Score was 23 (±11.4). Of the total patients, 82% were male and 91.6% sustained blunt trauma. Mean length of stay was 25 (±32.1) days. Anatomic areas injured included thorax (37%), lower leg/femur (38%), pelvis/acetabulum (22%), and spine (30%). The diagnosis was confirmed radiographically in 91 patients; two pulmonary emboli were confirmed at autopsy and one, despite a negative CT scan, was treated based on clinical suspicion. Of these 94 patients diagnosed with a PE, the PE was detected by angiogram in 5 (5%), ventilation/perfusion scan in 10 (11%), and computed tomography scan in 76 (81%). PE was diagnosed on day 1 to 4 in 35 patients (37%), on day 5 to 7 in 17 patients (18%), on day 8 to 14 in 22 patients (23%), and after 14 days in 20 patients (21%). Eleven percent died, but only two deaths were attributed to PE.

Conclusion: PE remains relatively common after trauma and occurs in the absence of lower extremity or spinal fractures. Although PE is usually thought to occur between days 5 and 7 after injury, our data suggest that as many as 37% of pulmonary emboli occur early. Clinicians should consider PE in the differential for patients with unexplained hypoxia, even early after injury.

Key Words: Pulmonary embolism, Injury, Incidence, Diagnosis modality, Timing.


Pulmonary embolism (PE) is a major cause of morbidity and mortality. It is estimated that as many as 500,000 to 600,000 cases of PE occur each year in the United States and it is the cause of death in approximately 50,000 to 200,000 patients a year.1 The association between injury and PE is well recognized. Traditional teaching has been that PE does not occur early after injury and has led physicians to have a lower index of suspicion during this time period. This low index of suspicion has minimized the workup for PE and early hypoxia and tachycardia have been attributed to other factors during the first few days after trauma. The purpose of this study was to analyze the timing of pulmonary emboli after trauma and the incidence of death directly related to the PE.

METHODS

This is a retrospective chart review performed at the R Adams Cowley Shock Trauma Center, University of Maryland Medical Center, Baltimore, MD. The trauma registry was reviewed for all patients diagnosed with a PE between June 1999 and December 2004. Data collected included demographics; past medical history; whether the patient was a primary admission, readmission or transfer admission; mechanism of injury; associated injuries or operations; symptoms prompting PE evaluation; Injury Severity Score; methods of prophylaxis use; results of deep venous thrombosis (DVT) results; the diagnostic test used to analyze PE; timing of PE from injury; treatment modality; discharge disposition; and outcome. The institutional review board at the University Maryland School of Medicine approved this study.

RESULTS

There were 35,424 patients admitted to our trauma center during the study period. One hundred and fourteen patients (0.32%) were diagnosed with PE. Twenty patients were excluded for a number of reasons: 14 patients had no radiographic evidence or chart documentation of PE, 2 patients had resident-read preliminary reads changed from positive to negative by attending staff, 2 patients had PE diagnosed at outside facilities before transfer to our facility, 1 patient was not admitted to the trauma center, and 1 patient had a negative angiogram after a positive CT scan and treatment was stopped. This resulted in 94 patients (0.27%) being diagnosed with a PE.

The mean day to diagnosis of PE was 11.8 days. Figure 1 demonstrates the time interval and percentage of PE diagnoses after injury. Of the 35 patients diagnosed with PE on
days 1 to 4, 14 (40%) were diagnosed within the first 2 days of hospitalization. The average age of the patients was 45 (±18.5; range, 16–90) years. A majority of the patients (n = 77; 82%), were men with an average age of 46 years; the 17 women (18%) had an average age of 44 years. Table 1 demonstrates the mechanism of injury as well as associated injuries. Of the 28 patients with a spinal column fracture (excluding transverse and spinous process), 15 had neurologic deficit. Seventy-two patients (76.6%) required at least one operative procedure. The mean Injury Severity Score was 23 (±11.4).

Prophylactic sequential compressive devices (SCDs) were used in 70 patients (74.5%). Of those, 58 (61.7%) had bilateral, and 12 (12.8%) had unilateral SCDs due to injury. Seventy-one patients (75.5%) had pharmacologic prophylaxis. Sixty patients (68%) used both a SCD and pharmacologic prophylaxis. Only one patient was documented as using neither a SCD nor pharmacologic prophylaxis. Of note, 16 charts were unable to be reviewed for information regarding mechanical and pharmacologic prophylaxis. Fifty-six patients (59.6%) had a PE during their initial primary admission. Fourteen (14.9%) returned from either home or a rehabilitation center, whereas 24 (25.5%) were transferred from an outside facility. Two (2.1%) patients received Recombinant Factor 7 before their diagnosis of PE.

Eighty-seven patients (92.6%) were symptomatic. The symptoms included tachypnea, tachycardia, or hypoxia, or a combination of the three, prompting evaluation for PE. Diagnosis of pulmonary emboli was analyzed by helical chest computed tomography (CT), pulmonary angiogram, ventilation/perfusion (V/Q) scan, postmortem or clinically. Figure 2 shows the percentage of PE detected by each modality. Sixty-nine patients (73.4%) were tested for deep vein thrombosis, of which nine tested positive. Forty-three patients (45.7%) were treated with intravenous unfractionated heparin, 13 patients (13.8%) were treated with low molecular weight heparin, and 19 patients (20.2%) were initially started on intravenous unfractionated heparin and subsequently converted to low molecular weight heparin. Eleven patients (11.8%) were not pharmacologically treated, four patients (4.3%) had other pharmacologic treatment regimens, and treatment was not determined in four patients (4.3%). Fifty-three patients (56.4%) had a vena cava filter placed. Of note, two patients were diagnosed with PE after placement of the vena cava filter.

Ten patients in our study (11%) had inhospital mortality. However, only two of those deaths can be directly attributed to a PE. The remaining deaths were caused by multisystem organ failure or withdrawal of care by family.

**DISCUSSION**

Almost 150 years ago, Virchow identified the classic triad of stasis, vascular damage, and hypercoagulability leading to venous thromboembolism (VTE) including PE. In 1967, Freeark demonstrated by the use of venography that trauma patients were susceptible to VTE including PE.² Despite the plethora of literature regarding the perceived rela-

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**Table 1** Demographics, Mechanism of Injury, and Associated Injuries

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45 (±18.5)</td>
</tr>
<tr>
<td>ISS</td>
<td>23 (±11.4)</td>
</tr>
<tr>
<td>Length of Stay</td>
<td>26 (±32.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>77</td>
<td>82</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Mortality</td>
<td>10</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism of injury</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor vehicle crash</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>Falls</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Motorcycle collision</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Gun shot wound</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Peds struck</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Injuries</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorax</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>Spine</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Lower leg</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Pelvis/Acetabulum</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Femur</td>
<td>15</td>
<td>16</td>
</tr>
</tbody>
</table>

LOS, length of stay; MVC, motor vehicle crash; GSW, gunshot wound.
tionship between trauma and PE, it remains a challenging diagnosis because of the nonspecific signs and symptoms. Trauma patients add additional difficulty in that many patients are comatose, intubated, or have disease that can provide adequate explanations for the various nonspecific signs of a PE.

Traditional teaching has been that pulmonary emboli occur most commonly between days 5 to 7 after injury and are rare before day 4. However, Owings et al. showed that as many as 23.8% of pulmonary emboli can occur in the first 4 days after injury and may occur on day 1. Sing et al. showed that more than half of pulmonary emboli diagnosed occurred in the first 7 days after trauma, whereas O'Malley et al. showed that 70% of the pulmonary emboli were diagnosed in the first 7 days after injury. Neither O'Malley et al. nor Sing et al. subdivide the first 7 days after injury, but O'Malley et al. commented on PE as early as 24 hours after injury. Our results show that 37% of our pulmonary emboli occurred within the first 4 days after trauma and 55% occurred in the first week after injury. More interestingly, 14 of the 35 pulmonary emboli diagnosed within the first 4 days after injury actually were diagnosed within the first 48 hours after injury. From this, we conclude that physicians must have a very high index of suspicion for PE from the time of admission after injury.

Before 1997 multiple authors had reported the incidence of PE after trauma ranging from 0.4% to 18%. Two reports in 1997 were published with a large patient population showing an incidence of 0.3%. Tuttle-Newhall et al. showed a 0.3% incidence of PE after trauma in 318,544 patients during a 6-year period. That same year, Owings et al. published a 0.35% incidence of PE after trauma in 18,255 patients during a 63-month period. Velmahos et al. did a meta-analysis of 73 studies and had a 1.5% pooled incident rate of PE after trauma. Our data showed a 0.27% incidence of PE consistent with Tuttle-Newhall et al. and Owings et al., which is lower than traditionally thought. In 2004, Knudson et al. published an analysis of over 450,000 patients and had an overall incidence of PE of 0.13%. Patients that had at least one risk factor had a PE rate of 0.21%. In 2005, Stawicki et al. demonstrated an incidence of PE of 0.5% in high risk patients (pelvic fracture, lower extremity fracture, severe head injury, or spinal cord injury) and an incidence of 0.2% in nonhigh risk trauma patients. Based on our study along with findings from recently published studies, it would appear that the incidence of PE after injury is not as high as previously thought.

Although our incidence of PE is consistent with recent studies, further analysis of the data shows an increase in diagnosis during the last 2 years of the study period. From years 2000 to 2002, 38 pulmonary emboli were radiographically detected. Year 2003 to 2004 yielded 53 radiographically proven pulmonary emboli. Of the 53 pulmonary emboli in years 2003 to 2004, 50 (94%) were detected using helical CT scan. During the previous 3 years, 19 (50%) were detected using helical CT scan. With advances in technology, fewer V/Q scans and pulmonary angiograms are being performed. The widespread availability of the newer generation helical CT scanner has enabled the evaluation for pulmonary emboli to occur much easier and quicker. Owings et al. diagnosed PE using either pulmonary angiogram or V/Q scan in 89% of their patients. No patient was evaluated using CT scan. Sing et al. diagnosed PE using helical CT scan in 64% of their patients, whereas 30% of patients were diagnosed using either pulmonary angiogram or V/Q scan. Overall, we diagnosed PE by using helical CT scan almost 81% of the time and using pulmonary angiogram and V/Q scan a combined 16% of the time. This is most likely a result of numerous factors. Twenty-four hour availability to advanced generation helical CT scan and 24-hour radiology coverage (18-hour attending, 6-hour resident) allows timely diagnosis.

At our institution, nuclear medicine as well as interventional radiology procedures often require calling a technician in from home after hours or outpatient scheduling, which can be problematic during daytime hours. The rapidness and availability at our institution of helical CT scan makes it the modality of choice for evaluating patients for PE. Based on the ease of obtaining CT scans at our institution, our faculty members are very aggressive about evaluating patients for PE and this may be a factor as to why pulmonary emboli are being diagnosed earlier after injury.

Published reports have mortality rates from PE ranging from 17% to 26%. Only one of the previously mentioned studies comment on PE being the direct cause of death. In Sing et al., of the 26 deaths (17.8%), they thought PE either contributed to or was the direct cause of death in 22 (15.1%) of the patients. In our study, of the 94 patients diagnosed with a PE, 10 deaths (11%) occurred. This is considerably lower than previously reported. Stated another way, the overall mortality in trauma patients with PE in our data is 0.028%. This coincides with Knudson et al.'s National Trauma Data Bank query of over 450,000, but is two to three times less often than in other studies. Of the 10 deaths in our study, only 2 (2.1%) contributed to or were the direct cause of death. This appears to be much lower than previously reported. Taking our data a step further, only 2 (0.005%) of 35,424 patients died as a result of a PE, which indicates that the overall incidence of mortality in trauma related to PE may in fact be much lower than previously thought.

One might conclude that we are finding many more pulmonary emboli that are not medically significant. Figure 3 demonstrates the locations of pulmonary emboli in our study and shows that a majority of pulmonary emboli were located in the main and lobar arteries. In addition, over 92% of patients were symptomatic, warranting evaluation for PE. Combining this information, it appears that most of the pulmonary emboli diagnosed were clinically significant. However, if the mortality directly related to PE is thought to be extremely low and treatment has many known risks and complications, do we need to look so hard? Patients who
develop PE, be it “small and clinically insignificant” or “clinically significant”, despite adequate prophylaxis, would seem to be at higher risk for developing additional and possibly fatal clot burden. Therefore, to delay aggressive workup, diagnosis, and treatment may not only increase the rate of mortality associated with PE after trauma but also increase morbidity associated with a longer hospital stay and increase overall costs.

Multiple studies have tried to elucidate risk factors for PE. In 2002, the Eastern Association for the Surgery of Trauma published their practice management guideline review for the risk factors of VTE after injury. The only level I recommendation they concluded was that patients with spinal cord injuries or spinal fractures were at high risk for VTE. Level II recommendations included risk factors that were more traditionally thought to be for VTE, including long bone fractures, pelvic fractures, and age, all of which had associations in single-institution studies but were not significant on meta-analysis. Table 1 reviews the absolute numbers of associated injuries in our study. Not having denominators for specific injuries may be misleading in stratifying risk of injuries associated with PE in our study. When reviewing a 3-year span during the data collection period and based on average number on injuries per year, it appears that femur fractures have a slightly higher association with PE than do spinal injuries and acetabulum/pelvic injuries (0.9% vs. 0.7%). When considering the magnitude of the denominator in our study population and the relatively small number of patients with the individual associated injury, a statistical difference between injuries cannot be appreciated.

Nine of our 94 patients with a PE were diagnosed with a deep vein thrombosis. Only 69 of our patients were tested for DVT, and only 10 of those had upper and lower extremities tested. The remainder had predominantly lower extremity duplex only. Of the patients tested, we had a 13% rate of simultaneous DVT and PE. This is almost identical to the results by Knudson et al., who demonstrated a simultaneous DVT and PE. This is almost identical to the duplex only. Of the patients tested, we had a 13% rate of mortality associated with PE after trauma but also increase morbidity associated with a longer hospital stay and increase overall costs.

An interesting observation from our data is that the relatively large percentage of patients diagnosed with a PE had intrathoracic trauma. Thirty-five (37%) of our patients either had rib fracture, pneumothorax, or hemothorax. It is conceivable to think that patients with intrathoracic injury have considerable pain and along with poor pulmonary status, decreased mobility ensues thus increasing the intuitive patient risk of PE. On the other hand, patients with intrathoracic injuries are often tachypnic, tachycardic, and hypoxic as a result of their underlying intrathoracic injury; however, the common symptoms may prompt caretakers to investigate for PE sooner. PE may be diagnosed in patients whose cause of symptoms was pneumonia or atelectasis. We think that patients with intrathoracic trauma who develop tachypnea, tachycardia, and hypoxia warrant an early workup for PE.

CONCLUSION

PE is a known complication after trauma. Our study results are similar to previously reported incidence of pulmonary emboli in trauma, approximately 0.3%. However, our data show that pulmonary emboli are common in the first 4 days after injury and that as many as 15% of them occur in the first 48 hours after injury. In addition, we found a considerably lower mortality rate (0.005%) directly related to PE than previously thought. Despite this lower mortality rate, concern for complications of a missed and untreated PE and the lack of prospective randomized double blind trials elucidating risk factors for PE, we strongly encourage the clinician to consider PE in the differential for patients with unexplained hypoxia and tachycardia, even early after injury.

REFERENCES


The Sensitivity of Computed Tomography (CT) Scans in Detecting Trauma: Are CT Scans Reliable Enough for Courtroom Testimony?

D. Kimberley Molina, MD, Joanna J. Nichols, BA, and Vincent J. M. DiMaio, MD

Background: Rapid and accurate recognition of traumatic injuries is extremely important in emergency room and surgical settings. Emergency departments depend on computed tomography (CT) scans to provide rapid, accurate injury assessment. We conducted an analysis of all traumatic deaths autopsied at the Bexar County Medical Examiner’s Office in which perimortem medical imaging (CT scan) was performed to assess the reliability of the CT scan in detecting trauma with sufficient accuracy for courtroom testimony.

Methods: Cases were included in the study if an autopsy was conducted, a CT scan was performed within 24 hours before death, and there was no surgical intervention. Analysis was performed to assess the correlation between the autopsy and CT scan results. Sensitivity, specificity, positive predictive value, and negative predictive value were defined for the CT scan based on the autopsy results.

Results: The sensitivity of the CT scan ranged from 0% for cerebral lacerations, cervical vertebral body fractures, cardiac injury, and hollow viscus injury to 75% for liver injury.

Conclusions: This study reveals that CT scans are an inadequate detection tool for forensic pathologists, where a definitive diagnosis is required, because they have a low level of accuracy in detecting traumatic injuries. CT scans may be adequate for clinicians in the emergency room setting, but are inadequate for courtroom testimony. If the evidence of trauma is based solely on CT scan reports, there is a high possibility of erroneous accusations, indictments, and convictions.

Key Words: Medical imaging, Sensitivity, Specificity, Autopsy correlation, Forensic testimony.

Rapid and accurate recognition of traumatic injuries is extremely important in emergency room and surgical settings. This information can help physicians to better triage patients and can dictate treatment options. If these decisions are being made on faulty presumptions, the outcomes can be disastrous. Traumatic emergency departments depend on computed tomography (CT) scans to provide rapid, accurate injury assessment. An extensive search of the English literature failed to reveal a study of the accuracy of CT and magnetic resonance imaging scans in detecting trauma, though a number of case reports exist of their weaknesses.1–7

In an attempt to generate the sensitivity and specificity of CT scans and to assess the reliability of the CT scans in detecting trauma of a sufficient accuracy for courtroom testimony, this study was devised to compare perimortem CT scans with autopsy findings.

MATERIALS AND METHODS

We conducted an analysis of all traumatic deaths autopsied at the Bexar County Medical Examiner’s Office in which perimortem medical imaging (CT scans) were performed during a 3.5-year time period (2002–2005). Cases were included in the study if an autopsy was conducted, a CT scan was performed within 24 hours before death, and there was no surgical intervention. At the time of autopsy, the medical examiners were blinded to the CT scan results.

CT scans were performed at one of three Level I trauma centers in San Antonio. All CT scans were reviewed by board certified radiologists. Images were acquired on helical CT scanners (HiSpeed Advantage, GE Medical Systems, Milwaukee, WI or Picker PQ or PQ 5000, Picker International, Cleveland, OH). Head images were obtained at a thickness of 5 mm at 5-mm intervals to the base of the skull (petrous ridges) and a thickness of 10 mm at 10-mm intervals to the vertex. Cervical spine images were obtained at a 3-mm thickness at a 2-mm interval. Chest, abdomen, and pelvis images were obtained at a 5-mm thickness at a 5-mm interval.

Analysis was performed to assess the correlation between the autopsy and CT scan results. Sensitivity (percentage of those with injury that have injury detected on CT scan[positive result]), specificity (percentage of those without injury that do not have any injury detected on CT scan[negative result]), positive predictive value (percentage of positive CT results that have injury), and negative predictive value (percentage of negative CT results that do not have injury) were defined for the CT scan based on the autopsy results.

RESULTS

One hundred and thirteen cases were identified that met study criteria. The study patients had an average age of 49.2
years with 39 women and 74 men and 107 white patients and 6 nonwhite patients. The majority of cases were either the result of head injuries caused by falls or multiple injuries caused by motor vehicle collisions. The 113 cases corresponded to a total of 398 injuries or injury groups.

**Head**

One hundred eleven of the 113 CT scan series included head scans, which corresponded to 295 injuries. Twenty-four of the scans correlated completely with the autopsy results, 21 scans did not correlate at all with autopsy results, and 66 scans had a partial correlation, meaning the CT scan documented some, but not all, of the injuries.

The sensitivity, specificity, positive predictive value, and negative predictive value of a CT scan for each type of injury is summarized in Table 1. As shown in Table 1, CT scans have the best sensitivity for subdural hematomas (66%) and the worst for basilar skull fractures (19%). The best specificity is for basilar skull fractures (100%), whereas the worst was for subarachnoid hemorrhage (SAH) (83%).

**Neck**

Twenty-eight of the 113 CT scan series included cervical scans, which corresponded to 14 injuries. Eighteen of the scans correlated completely with the autopsy results, 10 scans did not correlate at all with autopsy results, and there were no scans that showed partial correlation.

The sensitivity, specificity, positive predictive value, and negative predictive value of a CT scan for each injury type is summarized in Table 2. As shown in Table 2, the CT scan missed all five cases in which there was a fracture of a cervical vertebral body and had a 17% sensitivity and a 96% specificity in detecting dislocations of the cervical vertebrae.

**Chest, Abdomen, and Pelvis**

Seventy-eight of the 113 CT scan series included chest, abdomen, or pelvic scans, which corresponded to 89 injuries or injury groups. Forty-four of the scans correlated completely with the autopsy results, 18 scans did not correlate at all with autopsy results, and 16 scans had a partial correlation, meaning the CT scan documented some but not all injuries.

To assist in analysis, rib and pelvic fractures were grouped together as one injury group. For example, if the CT scan missed fractures of the left second through seventh ribs, this was treated as if it missed one injury, not six. Using this algorithm, the sensitivity, specificity, positive predictive value, and negative predictive value for chest, abdomen, and pelvic CT scans were generated and are summarized in Table 3. As shown in Table 3, the sensitivity of the CT scans ranged from 0% (cardiac and hollow viscus injury) to 75% (liver injury) with a specificity ranging from 86% (splenic injury) to 100% (sternal fractures, cardiac, and hollow viscus injury). Regarding the sternal fractures and the cardiac and hollow

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**Table 1** Correlation of Head CT Scans and Autopsy Findings

<table>
<thead>
<tr>
<th>Injury Type</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subdural hemorrhage (n = 73)</td>
<td>65.8</td>
<td>94.7</td>
<td>96.0</td>
<td>59.0</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage (n = 63)</td>
<td>44.4</td>
<td>83.3</td>
<td>77.8</td>
<td>53.3</td>
</tr>
<tr>
<td>Epidural hemorrhage (n = 6)</td>
<td>33.3</td>
<td>99.0</td>
<td>66.7</td>
<td>96.3</td>
</tr>
<tr>
<td>Cerebral contusion (n = 54)</td>
<td>31.5</td>
<td>94.7</td>
<td>85.0</td>
<td>59.3</td>
</tr>
<tr>
<td>Cerebral laceration (n = 7)</td>
<td>0</td>
<td>100.0</td>
<td>NA*</td>
<td>93.7</td>
</tr>
<tr>
<td>Basilar skull fracture (n = 37)</td>
<td>18.9</td>
<td>100.0</td>
<td>100.0</td>
<td>71.1</td>
</tr>
<tr>
<td>Cranial skull fracture (n = 18)</td>
<td>44.4</td>
<td>97.8</td>
<td>80.0</td>
<td>90.1</td>
</tr>
<tr>
<td>Occipital skull fracture (n = 11)</td>
<td>27.3</td>
<td>95.0</td>
<td>37.5</td>
<td>92.2</td>
</tr>
<tr>
<td>Diastatic skull fracture (n = 4)</td>
<td>0</td>
<td>100.0</td>
<td>NA*</td>
<td>96.4</td>
</tr>
<tr>
<td>Cerebral hemorrhage (SDH, EDH, SAH, contusion)</td>
<td>46.8</td>
<td>96.0</td>
<td>87.2</td>
<td>75.8</td>
</tr>
<tr>
<td>Skull fractures (occipital, basilar, diastatic, cranial)</td>
<td>25.7</td>
<td>98.1</td>
<td>72.0</td>
<td>87.6</td>
</tr>
</tbody>
</table>

n is the number of cases that were positive at autopsy for the listed finding.
* In no cases were cerebral lacerations or diastatic fractures documented by CT scan.
SDH, subdural hemorrhage; EDH, epidural hemorrhage.

**Table 2** Correlation of Neck CT Scans and Autopsy Findings

<table>
<thead>
<tr>
<th>Injury Type</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral fractures (n = 5)</td>
<td>0</td>
<td>100</td>
<td>NA*</td>
<td>82.1</td>
</tr>
<tr>
<td>Vertebral dislocations (n = 6)</td>
<td>16.7</td>
<td>95.5</td>
<td>50</td>
<td>80.8</td>
</tr>
</tbody>
</table>

n is the number of cases that were positive at autopsy for the listed finding.
* In no case was a cervical vertebral fracture documented by CT scan.
viscus injuries, in no case did the CT scan detect an injury when it was not actually present, giving a specificity of 100%. The CT scan failed to detect six of the eight sternal fractures, any of the four cases of cardiac injury, including cardiac contusions and transmural cardiac lacerations, or any of the five cases of hollow viscus injury, including perforations of the ileum, colon, and bladder, giving a sensitivity of 0% for cardiac and hollow viscus injuries and 25% for sternal injury.

**Fractures Overall**

Fractures occur throughout the body and were detected on every type of CT scan. To analyze the sensitivity of the CT scan in detecting fractures, the data from the head, neck, chest, abdomen, and pelvis were combined. Table 4 summarizes the values generated by combining the fracture data. As shown in Table 4, the overall sensitivity of the CT scan for detecting fractures is 29%, with a specificity of 95.5%, a positive predictive value of 62.5%, and a negative predictive value of 83.6%.

**DISCUSSION**

**Head Results**

The most devastating type of trauma is often head injury. Although head trauma is frequently not treatable, certain conditions can be, e.g., subdural hemorrhage, epidural hemorrhage. If these injuries are not correctly diagnosed, surgery can be delayed or even not performed, resulting in catastrophic consequences. The data from this study show that CT scans have less than 50% sensitivity for all types of head trauma, with the exception of subdural hemorrhages, where the sensitivity is 66%. The data show that in over half of the cases of head trauma, the trauma will be missed by the CT scan. Although the CT scan has acceptable specificities, ranging from 83% to 100%, the positive and negative predictive values are unacceptable. The negative predictive value for a subdural hematoma is 59%, meaning that if the CT scan did not disclose a subdural hematoma in a trauma case, there is a 41% chance that a subdural hematoma is actually present. Hart et al.\(^1\) have previously shown that, in children, subdural hemorrhage can also be missed on magnetic resonance imaging scans.

CT scans are even less reliable in detecting SAH, with 44% sensitivity, 83% specificity, 78% positive predictive value, and 53% negative predictive value. Although this study looked exclusively at cases of trauma, SAH can also be a result of nontraumatic events (e.g. a ruptured aneurysm); thus, its correct diagnosis is of the utmost importance to treatment and outcome. Kibayashi et al.,\(^2\) Spiegel et al.,\(^3\) and Chute and Smialek\(^4\) have proposed hypotheses as to why SAH is often misinterpreted on CT scans. They proposed that the density or vascularity of the dura\(^2,^4\) and anoxia\(^4\) could each be visualized on CT scans as SAH. However, none of these authors address the CT scans inability to detect SAH.

**Table 3 Correlation of Chest, Abdomen, and Pelvic CT Scans and Autopsy Findings**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rib fractures (n = 22 groups)</td>
<td>45.5</td>
<td>90.5</td>
<td>83.3</td>
<td>61.3</td>
</tr>
<tr>
<td>Sternal fractures (n = 8)</td>
<td>25.0</td>
<td>100</td>
<td>100</td>
<td>85.4</td>
</tr>
<tr>
<td>Thoracic and lumbar vertebral body fractures (n = 5)</td>
<td>40.0</td>
<td>93.2</td>
<td>28.6</td>
<td>95.8</td>
</tr>
<tr>
<td>Pelvic fractures (n = 9 groups)</td>
<td>55.6</td>
<td>88.5</td>
<td>62.5</td>
<td>85.2</td>
</tr>
<tr>
<td>Liver injury (n = 4)</td>
<td>75.0</td>
<td>90.3</td>
<td>50.0</td>
<td>96.6</td>
</tr>
<tr>
<td>Splenic injury (n = 6)</td>
<td>50.0</td>
<td>86.2</td>
<td>42.9</td>
<td>89.3</td>
</tr>
<tr>
<td>Cardiac injury (n = 4)</td>
<td>0</td>
<td>100</td>
<td>NA*</td>
<td>90.7</td>
</tr>
<tr>
<td>Solid organ injury, includes pancreas, kidney, liver, spleen (n = 16)</td>
<td>43.8</td>
<td>86.4</td>
<td>43.8</td>
<td>86.4</td>
</tr>
<tr>
<td>Hollow viscus injury, includes intestines and bladder (n = 5)</td>
<td>0</td>
<td>100</td>
<td>NA*</td>
<td>93.6</td>
</tr>
</tbody>
</table>

n is the number of cases that were positive at autopsy for the listed finding. * In no cases were cardiac or hollow viscus injuries documented by CT scan.

**Table 4 Correlation of Chest, Abdomen, and Pelvic CT Scans and Autopsy Findings**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral body fractures (n = 10)</td>
<td>20.0</td>
<td>94.8</td>
<td>28.6</td>
<td>91.9</td>
</tr>
<tr>
<td>Fractures, not incl. skull (n = 57)*</td>
<td>35.1</td>
<td>75.5</td>
<td>62.5</td>
<td>50</td>
</tr>
<tr>
<td>Skull fractures (n = 70)</td>
<td>25.7</td>
<td>98.1</td>
<td>72.0</td>
<td>87.6</td>
</tr>
<tr>
<td>Fractures overall (n = 127)*</td>
<td>29.9</td>
<td>95.5</td>
<td>66.7</td>
<td>81.9</td>
</tr>
</tbody>
</table>

n is the number of cases that were positive at autopsy for the listed finding. * The total number of fractures includes cervical dislocations and hyoid bone fractures.
This study shows that in almost half of cases where the CT scan does not detect SAH hemorrhage, SAH is present.

The CT scan is also not sensitive in detecting cerebral contusions (32% sensitivity) and lacerations (0% sensitivity). Although these injuries may not have a particular treatment option, the presence of the injuries may indicate injury type or severity, especially in cases where the person survives the injury and legal proceedings are forthcoming. For instance, in the case of the alcoholic who is found unconscious in front of a drinking establishment, the presence or absence and location of cerebral contusions could help substantiate whether the patient was assaulted or simply fell.

The skull fracture data supports the findings of Sumu-vuori et al.\(^5\) that CT scans are insensitive in detecting skull fractures. The overall sensitivity of the CT scan at detecting skull fractures was 26%. Cranial skull fractures are correctly detected 44% of the time, followed by occipital (27%), and basilar fractures (19%). For basilar skull fractures, although the CT scan is rarely able to detect them, the positive predictive value of a basilar skull fracture by CT is 100%; meaning that if a skull fracture is seen on a CT scan, it is real. Unfortunately, the same is not true for cranial and occipital fractures, where the positive predictive values are 80% and 38%, respectively.

**Neck Results**

As shown in Results, CT scans of the cervical spine are not very sensitive. For detecting cervical vertebral body fractures, CT scans have a sensitivity of 0% and for vertebral dislocations the sensitivity was 17%. Although the specificity was high, because most cases were negative for injury by both CT and autopsy, the negative predictive value of a cervical CT scan was 81% to 82%. Sweeney et al.\(^6\) also reported on three cases of cervical fractures that were discovered at autopsy and missed by CT scans.

Given the possible implications of a cervical vertebral body fracture, and its clinical and prognostic importance, we think that a CT scan of the cervical spine is too inaccurate to correctly detect disease.

**Body Results**

The sensitivity of the CT scan for chest, abdomen, and pelvic injuries ranged from 25% to 75%. The CT scan was most sensitive at detecting liver injuries (75%) and pelvic fractures (56%); but for all other injuries, the CT scan had a sensitivity of less than 50%. The specificities of the CT scan were better, with a range from 86% to 100%, with the highest specificities for sternal fractures, cardiac injuries, and hollow viscus injuries. However, in all of these cases, the specificities were 100% because in no case was an injury actually detected by CT scan. The corresponding negative predictive values were 85%, 85%, and 86%, respectively. Although these numbers may seem high, consider the reciprocal: in 15% of cases of a negative CT scan, there may be a transmural cardiac laceration, a most likely fatal injury unless rapid and correct diagnosis leads to appropriate therapy. Although the presence or absence of a sternal fracture, rib fractures, or even pelvic fractures may not be immediately life-threatening, cardiac injuries and hollow viscus perforations are potentially treatable, life-threatening injuries, but these must be correctly diagnosed to be treated appropriately.

Some injuries were also incorrectly detected by CT scans, meaning they were seen on CT but were not actually there. The positive predictive value for CT scans in correctly detecting chest, abdominal, and pelvic injuries ranged from 29% to 100%, with the highest rates being for sternal fractures (100%) and rib fractures (83%). This indicates that if sternal fracture and rib fracture are seen on CT they are most likely there; however, both of these injuries are not often seen on CT scans (25% and 45% sensitivity, respectively). The positive predictive value for vertebral fractures was 29%, indicating that in the majority of cases where a CT scan detects a fracture in a thoracic or lumbar vertebrae, it is not actually present.

More importantly, from a clinical perspective, may be the negative predictive value, meaning how often is a negative CT scan really negative? The negative predictive value ranged from 61.3% (rib fractures) to 97% (liver injuries), with most values ranging between 85% and 92%. As with neck injuries, although these numbers seem reasonable, it means that in 10% to 15% of cases CT scans will report no injuries when injuries are present.

**Fracture Results**

The overall sensitivity of the CT scan in detecting fractures was 29.1% with a range from 20% to 35%, which shows that the CT scan is not a valid method for the detection of fractures. The overall positive predictive value for fracture detection was 67%, which means that not only is the CT scan insensitive for detecting fractures, but in over 30% of cases, the CT scan will detect a fracture that is not there. As previously discussed regarding cervical fractures, the failure to accurately diagnose a fracture, may lead to inappropriate or inadequate treatment, and, as in the case of cervical vertebral body fractures, may have more devastating consequences.

**CONCLUSION**

The authors of this article are forensic pathologists whose primary interest is the accuracy and reliability of using CT scans for forensic purposes. The objective of this article is not to address the clinical utility of CT scans. The objective of this article is one of forensic importance. In the field of forensic pathology, CT scans are inadequate to detect trauma where a specific injury, though clinically insignificant, may be extremely relevant. This study reveals that CT scans are an inadequate detection tool for forensic purposes. In the forensic medical setting, a definitive diagnosis and an accurate description of injuries must be known with certainty, for instance, whether subarachnoid hemorrhage or subdural hemorrhage, cortical contusions, or skull fractures are present can
be of importance in determining not only cause, but manner of death.

The shortcomings of the CT scan must be known and understood by clinicians as well because it is often that the victim of trauma survives the event and an autopsy is never performed. If an autopsy is performed, the accuracy of CT scans is irrelevant for forensic diagnostic purposes. It is when the autopsy is not performed and postmortem diagnoses are made on the basis of CT scans that problems will arise in the validity of the diagnoses and conclusions. Even more serious problems arise when an individual does not die and the diagnosis of alleged injuries or absence of injuries is based on CT scans. Criminal indictments are lodged on the basis of a CT report that trauma has occurred. This is seen most commonly in young children (<3 years) where an accurate history cannot be elicited even if they fully recover from their trauma. Children are said to have incurred or not incurred, intentional or accidental, head injuries on the basis of CT scans. As we have demonstrated, CT scans have a low rate of accuracy and sensitivity in adults. If this is true for children, and we know no reason that it should not be, there is a high possibility of erroneous accusations, indictments, and convictions.

The standards in forensic cases are, by definition, higher than the standards in a clinical setting. In the clinical setting, doctors can treat the patient but in a court of law, absolutes are the measure of accuracy.

REFERENCES
Computed Tomography for Early and Safe Discontinuation of Cervical Spine Immobilization in Obtunded Multiply Injured Patients

Henry Thomas Stelfox, MD, PhD, George C. Velmahos, MD, PhD, Elise Gettings, RN, Luca M. Bigatello, MD, and Ulrich Schmidt, MD, PhD

Background: Evaluation of the cervical spine (c-spine) in obtunded severely injured trauma patients is controversial, and spine immobilization is frequently prolonged. We examined the effect of two different c-spine evaluation protocols on c-spine immobilization and clinical outcomes.

Methods: We prospectively evaluated consecutive intubated and mechanically ventilated patients admitted to the surgical intensive care unit (ICU) of a Level I academic trauma center with a diagnosis of multiple blunt injuries who had normal findings on high-resolution helical computed tomogram of C1 to T1 with reconstructions (HCTrecon). From July 1, 2003 to June 30, 2005 (n = 140), the findings of HCTrecon and either clinical examination or magnetic resonance imaging (MRI) were required to be normal to discontinue c-spine immobilization (clinical/MRI protocol). From July 1, 2005 to June 30, 2006 (n = 75), the policy was changed to require normal finding only on HCTrecon to discontinue c-spine immobilization (HCTrecon protocol).

Results: Patients evaluated by the clinical/MRI and HCTrecon protocols had similar baseline characteristics. Compared with clinical/MRI patients, HCTrecon patients had their c-spines immobilized for fewer days (median, 6 days vs. 2 days; \( p < 0.001 \)), were less likely to experience a complication of c-spine immobilization (64% vs. 37%, \( p = 0.010 \)), required shorter periods of mechanical ventilation (median, 4 days vs. 3 days; \( p = 0.011 \)), and had shorter stays in the ICU (median, 6 days vs. 4 days; \( p = 0.028 \)) and hospital (median, 16 days vs. 14 days; \( p = 0.043 \)). There was no difference in hospital mortality (13% vs. 16%, \( p = 0.920 \)) and no missed c-spine injuries in either group.

Conclusion: Discontinuation of c-spine precautions based on the normal findings of HCTrecon decreases the duration of c-spine immobilization in obtunded severely injured patients and is associated with fewer complications, fewer days of mechanical ventilation, and shorter stays in the ICU and hospital.

Key Words: Blunt trauma, Computed tomography, Spinal injury, Spinal immobilization, Cervical collar.
2003 and June 30, 2005, the hospital’s trauma program followed a protocol for evaluation of the c-spine of obtunded blunt trauma patients with multiple injuries whereby c-spine immobilization could be discontinued after (1) a normal finding on HCTrecon and (2) any of the following: a normal finding in clinical examination, on MRI within 48 hours of injury, or on passive flexion-extension images. This was labeled as the clinical/MRI protocol. The c-spine evaluation protocol was changed on July 1, 2005. According to the new protocol, c-spine immobilization could be discontinued after a normal finding on HCTrecon, with no need for additional tests or clinical examination. The findings of HCTrecon were considered normal only if an attending radiologist and the treating attending trauma surgeon agreed that no direct (fracture, dislocation, subluxation) or indirect (soft tissue edema, inappropriate lordosis, widening of atlantoaxial interval) signs of injury existed. This was labeled as the HCTrecon protocol.

**Patients**

We included consecutive intubated and mechanically ventilated patients 16 years of age or older who were admitted to the Surgical ICU with a diagnosis of multiple blunt injuries between July 1, 2003 and June 30, 2006 and had a normal finding on HCTrecon of C1 to T1 as part of their trauma evaluation. Patients who were not intubated, had penetrating injuries, or were admitted to other ICUs were excluded.

Characteristics of the patients and their injuries were obtained from the medical and trauma registry records. Patient comorbidities were summarized using the Charlson morbidity index. Injuries were characterized by mechanism (blunt or penetrating) and anatomic severity (Injury Severity Score).

**Study Measures**

We defined the primary outcome measures as (1) duration of c-spine immobilization, (2) complications of c-spine immobilization, (3) missed c-spine injuries, (4) duration of mechanical ventilation, and (5) length of ICU and hospital stay. The duration of c-spine immobilization was defined as the time from hospital admission to the placement of an order to discontinue immobilization. We included two types of complications of c-spine immobilization: (a) those directly associated with immobilization such as pressure ulcers, and (b) those hypothesized to be indirectly associated with immobilization such as health-care-associated pneumonia (presumably caused by inadequate mobilization and physiotherapy), catheter-related complications (presumably caused by reduced anatomic exposure during catheter placement and increased bacterial colonization under the collar), delirium (presumably a result of patient discomfort and medications), and venous thromboembolic disease (presumably caused by prolonged immobility). A missed c-spine injury was defined as an injury diagnosed after cervical immobilization was discontinued. As secondary outcomes, we measured general processes of critical care and general complications of the critically ill trauma patient to evaluate whether the patients and parameters of care changed during the study period. In this way, we sought to understand whether differences in primary outcomes found between the two protocol periods could be attributed to the change in c-spine protocols or to changes in other parameters unrelated to these protocols. The parameters of process of care included venous thromboembolism prophylaxis, stress ulcer prophylaxis, and serum glucose control. The categories of general complications of critically ill trauma patients included operative, medical procedure related, drug related, supportive-care related, and miscellaneous.

A trained medical record analyst (E.G.) de-identified each patient’s hospital discharge summary of names, dates, and protocols used in evaluating the c-spine. Two independent physicians (H.T.S., U.S.), blinded to the c-spine evaluation protocol, reviewed each patient’s records summary for complications. Discrepancies were resolved with discussion.

**Statistical Analyses**

In the primary analysis, we compared two patient groups for baseline characteristic and outcome measures: the group managed by the clinical/MRI protocol (July 1, 2003–June 30, 2005) and the group managed by the HCTrecon protocol (July 1, 2005–June 30, 2006). We performed a secondary analysis to look for a dose-response relationship between the duration of c-spine immobilization, classified into tertiles, and the study measures. Baseline patient characteristics were compared using Student’s t test for continuous variables, and Fisher’s exact tests for categorical variables. Agreement on complication evaluations was assessed with Cohen \( \kappa \) reliability coefficient. Linear and logistic regression analyses were used to test for differences between patients evaluated using the clinical/MRI and HCTrecon protocols after adjustment for demographic (age, gender, race), hospital (transfer), and clinical (Charlson Index score, blood alcohol, toxicology screen, mechanism of injury, Injury Severity Score, first hematocrit in the emergency department) characteristics. Nonparametric comparisons were performed using the Mann-Whitney test. Statistical analyses were performed using Stata (Version 9.0; Stata Corp., College Station, TX) with two-tailed significance levels of 0.05.

**RESULTS**

Of 5,401 patients with multiple blunt injuries admitted between July 1, 2003 and June 30, 2006, 215 patients satisfied the inclusion criteria (Fig. 1). One hundred forty patients were evaluated during the clinical/MRI protocol period, and 75 were evaluated during the HCTrecon protocol period. Two patients had missing trauma registry records (both HCTrecon protocol). Medical records were available for the remaining 213 patients (99%). The \( \kappa \) coefficients for the presence of...
complications of c-spine immobilization and critical illness were 0.73 and 0.43, respectively.

The baseline characteristics of the study groups were similar (Table 1). Cervical spine immobilization was discontinued before death or hospital discharge in 128 (91%) clinical/MRI patients and 70 (93%) HCTrecon patients ($p = 0.885$). The duration of immobilization was 4 days shorter for HCTrecon patients compared with for clinical/MRI patients ($p < 0.001$) (Table 2). Overall, there were 186 complications in 117 patients secondary to c-spine immobilization. Patients evaluated with the HCTrecon protocol were 67% less likely to experience a complication secondary to c-spine immobilization compared with the clinical/MRI protocol patients ($p = 0.010$) (Table 2). This difference reflected pressure ulcers ($p = 0.018$), delirium ($p = 0.003$), and health-care–associated pneumonia ($p = 0.065$). No missed c-spine injuries were documented in either group.

Compared with the clinical/MRI group, the HCTrecon group had fewer days of mechanical ventilation (median, 4 days vs. 3 days; $p = 0.011$). No differences in hospital mortality (13% vs. 16%, $p = 0.920$) or in the number of patients discharged home (32% vs. 40%), to rehabilitation facilities (61% vs. 57%), or other health-care facilities (7% vs. 3%) were observed ($p = 0.411$ for test of proportions). Patients in the HCTrecon group had shorter stays in the ICU (median, 6 days vs. 4 days; $p = 0.028$) and hospital (median, 16 days vs. 14 days; $p = 0.043$).

We observed no differences between the clinical/MRI and HCTrecon protocols when we examined general processes of care and complications that might be related to unmeasured characteristics of the patients and changes in surgical critical care (Table 3). The majority of patients in both groups received deep venous thrombosis prophylaxis, stress ulcer prophylaxis, and moderate glycemic control. No differences were observed in the incidence of general complications. Operative complications were most common followed by complications of supportive care (e.g., urinary tract infections and hypernatremia) and drug-related complications.

The duration of c-spine immobilization for patients in both the clinical/MRI and HCTrecon groups was positively

Fig. 1. Patients in the study.
associated with the incidence of complications during hospitalization \( (p < 0.001) \), duration of mechanical ventilation \( (p < 0.001) \), length of ICU stay \( (p < 0.001) \), and length of hospital stay \( (p < 0.001) \) (Fig. 2).

**DISCUSSION**

Our study examined two protocols for evaluating the c-spine in obtunded blunt trauma patients with multiple injuries; a clinical/MRI protocol and an HCTrecon protocol.

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**Table 1 Baseline Characteristics of the Patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Clinical/MRI Protocol (N = 140)</th>
<th>HCTrecon Protocol (N = 75)</th>
<th>( p^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, yr</td>
<td>42.9 ± 18.8</td>
<td>45.5 ± 20.0</td>
<td>0.347</td>
</tr>
<tr>
<td>Female</td>
<td>36 (26)</td>
<td>22 (29)</td>
<td>0.569</td>
</tr>
<tr>
<td>Nonwhite race</td>
<td>23 (18)</td>
<td>20 (26)</td>
<td>0.112</td>
</tr>
<tr>
<td>Charlson comorbidity index score, mean ± SD</td>
<td>0.8 ± 1.5</td>
<td>0.7 ± 1.2</td>
<td>0.850</td>
</tr>
<tr>
<td>Transferred from another institution</td>
<td>58 (41)</td>
<td>30 (40)</td>
<td>0.900</td>
</tr>
<tr>
<td>Ethanol screen positive†</td>
<td>52 (43)</td>
<td>27 (43)</td>
<td>0.951</td>
</tr>
<tr>
<td>Toxicology screen positive‡</td>
<td>51 (42)</td>
<td>18 (37)</td>
<td>0.591</td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Road traffic injuries</td>
<td>102 (73)</td>
<td>54 (73)</td>
<td></td>
</tr>
<tr>
<td>Falls</td>
<td>27 (19)</td>
<td>15 (20)</td>
<td></td>
</tr>
<tr>
<td>Violent injuries</td>
<td>8 (6)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>Other injuries</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Injury Severity Score, mean ± SD</td>
<td>23.6 ± 13.1</td>
<td>25.3 ± 13.6</td>
<td>0.377</td>
</tr>
<tr>
<td>Head/neck AIS, mean ± SD</td>
<td>4.1 ± 0.8</td>
<td>4.0 ± 0.8</td>
<td>0.570</td>
</tr>
<tr>
<td>Face AIS, mean ± SD</td>
<td>2.1 ± 0.5</td>
<td>2.1 ± 0.5</td>
<td>0.821</td>
</tr>
<tr>
<td>Chest AIS, mean ± SD</td>
<td>3.4 ± 0.9</td>
<td>3.5 ± 1.1</td>
<td>0.641</td>
</tr>
<tr>
<td>Abdomen/pelvis AIS, mean ± SD</td>
<td>2.6 ± 0.8</td>
<td>2.8 ± 1.0</td>
<td>0.449</td>
</tr>
<tr>
<td>Extremities AIS, mean ± SD</td>
<td>2.7 ± 0.5</td>
<td>2.8 ± 0.5</td>
<td>0.100</td>
</tr>
<tr>
<td>External AIS, mean ± SD</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0</td>
<td>0.494</td>
</tr>
<tr>
<td>First ED hematocrit, mean ± SD</td>
<td>38.1 ± 6.1</td>
<td>37.3 ± 7.3</td>
<td>0.412</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) unless otherwise indicated.

\( ^* \) \( p \) values for the comparison between the clinical/MRI and HCTrecon protocol groups were calculated by Student’s \( t \) test, \( \chi^2 \) test, or Fisher’s exact test.

† Ethanol screen was performed on 120 patients and 63 patients during the clinical/MRI and HCTrecon protocol periods, respectively.

‡ Toxicology screen was performed on 120 patients and 49 patients during the clinical/MRI and HCTrecon protocol periods, respectively.

AIS, Abbreviated Injury Score.

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**Table 2 Evaluation of the Cervical Spine and the Complications of Immobilization**

<table>
<thead>
<tr>
<th>Measures</th>
<th>Clinical/MRI Protocol (N = 140)</th>
<th>HCTrecon Protocol (N = 75)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical spine evaluation( ^* )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of cervical spine immobilization, median (interquartile range), d</td>
<td>6 (3–13.5)</td>
<td>2 (1–6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Method of cervical spine evaluation( ^† )</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCTrecon</td>
<td>13 (10)</td>
<td>55 (80)</td>
<td></td>
</tr>
<tr>
<td>HCTrecon plus clinical examination</td>
<td>104 (81)</td>
<td>9 (13)</td>
<td></td>
</tr>
<tr>
<td>HCTrecon plus MRI</td>
<td>7 (5)</td>
<td>6 (9)</td>
<td></td>
</tr>
<tr>
<td>HCTrecon plus flexion and extension images</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Complication of cervical spine immobilization( ^‡ )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any complication</td>
<td>89 (64)</td>
<td>28 (37)</td>
<td>0.010</td>
</tr>
<tr>
<td>Pressure ulcers</td>
<td>10 (7)</td>
<td>0 (0)</td>
<td>0.018</td>
</tr>
<tr>
<td>Delirium</td>
<td>68 (49)</td>
<td>20 (27)</td>
<td>0.003</td>
</tr>
<tr>
<td>Health care associated pneumonia</td>
<td>48 (34)</td>
<td>15 (20)</td>
<td>0.065</td>
</tr>
<tr>
<td>Catheter-related complications</td>
<td>8 (6)</td>
<td>1 (1)</td>
<td>0.303</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>11 (8)</td>
<td>5 (7)</td>
<td>0.373</td>
</tr>
<tr>
<td>Missed cervical spine injury</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) unless otherwise indicated.

\( ^* \) \( p \) values for the comparison between the clinical/MRI and HCTrecon protocol groups were calculated by Mann-Whitney \( U \) test and Fisher’s exact test.

\( ^† \) Cervical spine immobilization was discontinued before death or hospital discharge in 128 patients and 70 patients in the clinical/MRI and HCTrecon protocol groups, respectively.

\( ^‡ \) Comparisons between the clinical/MRI and HCTrecon protocol groups are adjusted for patient baseline characteristics.
The results demonstrate that discontinuing c-spine precautions based on a normal HCTrecon decreases the duration of c-spine immobilization and is associated with fewer pressure ulcers, less delirium, fewer cases of health-care–associated pneumonia, fewer days of mechanical ventilation, and shorter stays in the ICU and hospital.

The decision to discontinue c-spine precautions in the obtunded blunt trauma patient with multiple injuries is difficult because it requires an assessment of the risks of a missed c-spine injury against the morbidity of prolonged cervical immobilization. Previous case reports and case series have documented pressure ulcers,10,11 airway problems,23 catheter-related complications,14 failed enteral nutrition,24 and difficulties in managing elevated intracranial pressure in patients with c-spine immobilization.25 Our study provides the strongest evidence to date that c-spine immobilization is associated with delirium and hospital-associated pneumonia. Although we observed no mortality differences in the c-spine evaluation protocols in our study, delirium and hospital-associated pneumonia have both been associated with increased mortality in critically ill patients.16,26 Furthermore, our results demonstrate that the morbidity associated with c-spine immobilization increases with the duration of immobilization, highlighting the need for early and safe discontinuation of c-spine precautions.

The choice of which diagnostic tests to use in evaluating the c-spine of the obtunded blunt trauma patient with multiple injuries is difficult because of ongoing scientific debate and wide practice variation.4 CT of the c-spine has been established as the most sensitive, specific, and cost-effective

Table 3 General Processes of Care and Complications in Critically Ill Trauma Patients

<table>
<thead>
<tr>
<th>Measures</th>
<th>Clinical/MRI Protocol (N = 140)</th>
<th>HCTrecon Protocol (N = 75)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>General process of care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT prophylaxis, hospital day 1</td>
<td>128 (91)</td>
<td>67 (89)</td>
<td>0.628</td>
</tr>
<tr>
<td>Stress ulcer prophylaxis, hospital day 1</td>
<td>127 (91)</td>
<td>68 (91)</td>
<td>1.000</td>
</tr>
<tr>
<td>AM Blood glucose, hospital day 2, mean ± SD, mg/dL</td>
<td>146 ± 48</td>
<td>150 ± 45</td>
<td>0.957</td>
</tr>
<tr>
<td>Clinical complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any complication</td>
<td>27 (19)</td>
<td>16 (21)</td>
<td>0.805</td>
</tr>
<tr>
<td>Operative</td>
<td>11 (8)</td>
<td>9 (12)</td>
<td>0.316</td>
</tr>
<tr>
<td>Medical procedure-related</td>
<td>4 (3)</td>
<td>3 (4)</td>
<td>0.618</td>
</tr>
<tr>
<td>Drug-related</td>
<td>9 (6)</td>
<td>1 (1)</td>
<td>0.246</td>
</tr>
<tr>
<td>Supportive care failure</td>
<td>9 (6)</td>
<td>7 (9)</td>
<td>0.276</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2 (1)</td>
<td>2 (3)</td>
<td>0.355</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) unless otherwise indicated.

* Comparisons between the clinical/MRI and HCTrecon protocol groups are adjusted for patient baseline characteristics.

DVT, deep vein thrombosis.

Fig. 2. Duration of cervical spine immobilization and outcome measures. p < 0.001 for trend for all four study variables.
CONCLUSIONS

Obtunded and severely injured trauma patients will continue to challenge physicians with the evaluation and management of their c-spines. Our results suggest that the early evaluation and discontinuation of c-spine immobilization in patients with no evidence of injury will improve patient outcomes. HCTrecon as part of the initial trauma evaluation seems to be a safe and highly efficient evaluation strategy. Although c-spine evaluation is important it is rarely an emergency and should not distract clinicians from life-threatening injuries.

REFERENCES


Magnetic Resonance Imaging Is a Useful Adjunct in the Evaluation of the Cervical Spine of Injured Patients

Babak Sarani, MD, Sasha Waring, BS, Seema Sonnad, PhD, and C. William Schwab, MD

Background: Recognition of cervical spine (c-spine) injury is important to minimize the risk of disability. Yet the ideal method to detect injury remains controversial, especially in unexaminable patients. The purpose of this study was to evaluate the incidence of c-spine injury detected by magnetic resonance imaging (MRI) in patients with no abnormalities detected by computerized tomography (CT) scan and to determine whether the treatment plan was altered.

Materials: A retrospective study was performed on all patients who underwent both CT and MRI scanning of the c-spine in 2004 to 2005. Unexaminable patients formed a separate subgroup of the overall cohort. Patients were deemed to be unexaminable by the attending surgeon if their mental status remained depressed after intoxicants were judged to have been metabolized. CT and MRI scan findings were defined as normal if they were without any radiographic abnormality and showed only chronic degenerative changes.

Results: A total of 254 adult patients were included. Of these, 53 patients were unexaminable. Ninety patients showed abnormality on CT scan and were excluded from further analysis. MRI detected an injury in 42 of the remaining 164 patients whose CT scan disclosed nothing abnormal, 27 of which were ligamentous or cord injuries. The findings of the MRI resulted in surgery in 9, maintenance of the rigid cervical collar in 22, and discontinuance of the collar in 11 patients. In the unexaminable cohort, MRI detected an injury in 5 of 46 patients whose CT scan disclosed nothing abnormal, four of which were ligamentous and were treated by cervical collar immobilization.

Conclusion: This study supports the practice of obtaining c-spine MRI in patients who are either unexaminable or symptomatic with the CT scan findings normal.

Key Words: Cervical spine injury, MRI.

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From the Division of Traumatology and Surgical Critical Care, Department of Surgery, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania.
Address for reprints: Babak Sarani, MD, Department of Surgery, Division of Traumatology and Surgical Critical Care, University of Pennsylvania, 3440 Market St, First Floor, Philadelphia, PA 19104; email: saranib@uphs.upenn.edu.
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The Journal of TRAUMA® Injury, Infection, and Critical Care

The early accurate diagnosis of cervical spine (c-spine) injury is a crucial step in managing all injured patients. Previous reports suggest that there may be delay in the diagnosis of c-spine injury in up to 15% of patients and this may result in the development of a neurologic deficit after arrival to the hospital. An important aspect is the possibility that some patients whose c-spine computerized tomography (CT) scan findings disclosed nothing abnormal may have undetected, clinically significant injury. However, no consensus exists on the most accurate, safest, and cost- and time-effective modality to comprehensively evaluate the many components of the c-spine and detect all injury. This is especially important in the patient who is either unexaminable or for other reasons has an unreliable physical examination.

The purpose of this study was to retrospectively evaluate the incidence of c-spine injuries detected by magnetic resonance imaging (MRI) in patients whose CT scan of the c-spine disclosed no abnormalities. A second goal was to determine the incidence of c-spine injuries detected by MRI in unexaminable patients with no abnormal findings on the CT scan of the c-spine, and the third to determine the frequency with which the treatment rendered was affected by the results of the MRI.

PATIENTS AND METHODS

A retrospective review was performed after obtaining approval from the institutional review board in compliance with HIPAA (Health Insurance Portability and Accountability Act) regulations. The trauma registry was used to identify all patients presenting to the Hospital of the University of Pennsylvania in 2004 and 2005 who underwent both CT and MRI evaluations of the c-spine during their hospital visit. CT imaging was performed using a 16-slice multidetector scanner. The following information was collected from the medical record: age, date of arrival, mechanism of injury, Injury Severity Score (ISS), indication for MRI of the c-spine, results of CT and MRI scans of the c-spine, treatment plan after CT scan, and treatment given after MRI. CT and MRI scan findings of the c-spine were defined as normal if they were without any radiographic abnormality and showed only chronic degenerative changes as determined by an attending radiologist.

The clinical practice guidelines at the Hospital of the University of Pennsylvania require evaluation of the c-spine using CT scans in all trauma patients who are deemed to be unexaminable, are greater than age 65 years, and have pain,
tenderness, or neurologic deficit. Although CT scan is used to evaluate impaired patients (intoxicated or inebriated patients, or those with drug or substance in the blood stream or body tissues), MRI is not used to evaluate those with transient impairment. Rather, such patients are maintained in a rigid cervical collar and MRI is ordered if the patients have pain or an abnormal neurologic examination once they are no longer impaired. MRI is then used to evaluate for ligamentous injury in all patients who have persistent pain or tenderness, neurologic deficit, or persistently altered level of consciousness. Patients are deemed to be unexaminable by the attending surgeon if they have significant traumatic brain injury or their mental status remains depressed after drugs or intoxicants have been metabolized. Although the timing of the MRI is variable, most scans are obtained within 72 hours of arrival to the hospital.

RESULTS

A total of 5,473 adult patients were evaluated by the trauma service from January 2004 to December 2005. Of this group, 254 patients underwent both CT scan and MRI evaluation of the c-spine for one or more of the reasons noted in Figure 1. This group constitutes the overall study population. Of this group, 53 patients underwent imaging because they were unexaminable (Fig. 2). The average age in the overall and unexaminable groups was 42 years, and the average ISS in the overall and unexaminable groups was 18 and 27, respectively. An ISS >21 was associated with a MRI with abnormalities (p = 0.03). The top three mechanisms of injury in both cohorts were motor vehicle collision, fall, and pedestrian struck.

A c-spine injury was found by CT scan in 90 of 254 (35%) patients in the overall group. These patients were excluded from further analysis. MRI detected an injury in 42 (25%) of the remaining 164 patients whose CT scan disclosed no abnormalities (Table 1). Of note, MRI detected a cord or ligamentous injury in 27 of 164 (16%) of the patients with CT scan with no abnormal findings. Two of the 19 patients with Table 1 MRI Results of All Patients With No Abnormal CT Findings

<table>
<thead>
<tr>
<th>Nature of Injury</th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>122</td>
<td>74</td>
</tr>
<tr>
<td>Ligamentous injury*</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>12 Patients with interspinous ligament injury, 5 with anterior longitudinal ligament injury, 2 with posterior longitudinal ligament injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord injury</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>7 Patient with contusion, 1 with central cord</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Herniated disc</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Dislocation</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* Two patients had multicolumn ligamentous injury.

Fig. 1. Indications for MRI and findings in the overall group. *Patients had at least one of the noted indications for MRI. **See Figure 2.
ligamentous injury had multicolumn, unstable injuries, and the other 17 patients had single column injuries. The findings on the MRI evaluation resulted in a change in therapy in 31 of 164 patients in this group (19%). The change in therapy involved surgery in 9 patients, maintenance of the rigid cervical collar for 6 weeks in 22 patients, and discontinuance of the cervical collar in 11 patients. The indication for surgery was unstable ligamentous injury in two patients and cord compression with or without herniated disc in the others.

For the unexaminable cohort, a c-spine injury was detected by CT scan in 7 of 53 patients (13%). MRI detected an additional injury in 5 of 46 patients (11%) whose CT scan disclosed no abnormalities (Table 2). Four of these patients (80%) were noted to have ligamentous injury (2 anterior longitudinal ligament, 2 interspinous ligament) and one was found to have a herniated disc. Thus, the CT scan was found to have 50% sensitivity in detecting soft tissue injuries of the c-spine in this patient population. The findings of the MRI evaluation resulted in a change in therapy in four of five of these patients in that they were maintained in a rigid cervical collar for 6 weeks. The one patient noted to have a herniated disc had his cervical immobilization discontinued.

**DISCUSSION**

The overall incidence of c-spine injury was 2%, with most injuries resulting from blunt trauma. Patients with pain during range of motion, tenderness on physical examination, or age > 65 years are at increased risk of having a clinically significant c-spine injury. Furthermore, those who cannot cooperate with physical examination are at increased risk of having a missed injury or a delay in the diagnosis of such injuries.

There is variability in the method of evaluation for patients with pain on active range of motion, tenderness on physical examination, or subtle neurologic deficits, such as paresthesia. Despite published clinical practice guidelines, no universally accepted practice has emerged. One guideline allows for maintenance of the patient in a rigid cervical collar and re-evaluation in 2 weeks in cases where patients have pain only. Some centers follow these guidelines and obtain further imaging only for persistent symptoms or neurologic deficit, whereas others use MRI or dynamic fluoroscopy to evaluate all patients whose CT scan findings were normal and had pain or deficit before discharge.

More worrisome as a common clinical problem is the evaluation and clearance of the c-spine in unexaminable trauma patients. Some authors recommend keeping the c-spine immobilized in a rigid collar until such time that the patient is examinable. However, this practice can lead to a number of problems including immobility, chin, chest and occipital decubitis, and reluctance to perform certain operative procedures until spine clearance is obtained. Other investigators recommend the use of fluoroscopy with passive range of motion to detect c-spine ligamentous instability in patients without cervical fracture, though its sensitivity and utility in obtunded patients remains controversial. Increasingly, many trauma centers rely on MRI to further assess the c-spine in obtunded patients because CT has a lower sensitivity for detecting cervical ligamentous injury relative to MRI. However, the high cost, physical isolation of the patient in the MRI suite, and the logistics of acquiring an urgent MRI scan have prevented more universal application to this problem. Because of this, some advocate using CT imaging alone to detect clinically significant c-spine injury with the assertion that absence of secondary signs, such as soft tissue edema or inflammation on the CT scan, is sufficient to exclude c-spine ligamentous injury.

Our study found a significant rate of c-spine injury that was evident only on MRI scanning. The findings of this study are especially relevant in unexaminable patients because this is the cohort that is not able to express signs or symptoms related to their injury and thus are prone to having a delay in diagnosis or missed injury. The injuries noted in this study are clinically significant despite the fact that they mostly involved one ligamentous column and thus are mechanically stable. Early detection of even minor injuries can prompt referral to physical therapy to minimize morbidity and reassure the patient, family, and employer as to the cause of disability from pain or tenderness. As has been shown for patients with back pain, patients with persistent symptomatic c-spine injury expect diagnostic testing and proof that their symptoms are real and an evidence-based treatment plan. Addressing these points during the patient’s initial admission may result in return to work with appropriate limitations on physical activity and provide the patient and all who care for him or her with a more objective and expected course to full recovery. In addition, the completeness of MRI can potentially minimize litigation for presumed delay in diagnosis or missed injuries. As importantly, MRI findings can result in discontinuation of the rigid cervical collar on many patients thereby avoiding the restrictions, discomfort, and even complications of prolonged use of a c-spine immobilization device.

Our findings contradict some reports suggesting that CT scan alone is sufficient to exclude all clinically relevant injuries and support others that show only 6% to 12% of...
ligamentous injuries are detected with CT scan alone. One possible reason for the differing conclusion among the various studies is that CT visualizes soft tissue poorly and relies on secondary signs of injury, such as edema and hematoma. These signs may not be present or visible on CT scan performed soon after injury.

This study has several weaknesses because of its retrospective nature. First, it was not possible to determine the exact signs or symptoms that prompted imaging studies in the examinable cohort. Furthermore, it was not possible to delineate the quantity or quality of the clinical information given to the radiologist and how this may have affected the interpretation of either the CT or MRI studies. The single center design and small sample size preclude the ability to extrapolate these findings to other centers.

In conclusion, this study supports the practice of obtaining MRI before definitively “clearing” the c-spine in patients who are either unexaminnable or symptomatic when the c-spine CT scan disclosed no abnormalities.

REFERENCES

Technical Considerations in the Operative Management of Femoral Neck Fractures in Elderly Patients: A Multinational Survey

Sanjeev Kakar, MD, MRCS, Paul Tornetta III, MD, Emil H. Schemitsch, MD, Marc F. Swiontkowski, MD, Kenneth Koval, MD, Beate P. Hanson, MD, MPH, Anders Jönsson, PhD, and Mohit Bhandari, MD, MSc, FRCSC, On Behalf of the International Hip Fracture Research Collaborative

Objective: To identify current opinions among orthopedic traumatologists relating to technical aspects of internal fixation and arthroplasty for patients with femoral neck fractures.

Methods: We developed and administered a survey to orthopedic surgeons who were members of the Orthopedic Trauma Association and European clinics affiliated with AO International (Davos, Switzerland). Surgeons reported preferences in specific aspects of the surgical technique for internal fixation as well as arthroplasty. Each surgeon received either a mailed package (7-page survey, a personalized cover letter, and a stamped return envelope) or an email with a link to the same survey on the Internet with an identification code. At 6 weeks, 12 weeks, and 18 weeks after the initial mailing, we remailed the questionnaire to all nonresponders.

Results: Of the 442 surgeons who were sent the questionnaire, 298 (68%) responded. The typical respondent was a North American aged more than 40 years, in academic practice, supervised residents, had fellowship training in trauma, and worked in a low-volume center. Among surgeons who treated displaced femoral neck fractures with arthroplasty, significant disparities existed in terms of the type of anesthesia (51% preferring general anesthesia), surgical approach (47% used posterior approach), and placement of unipolar implants (50%). Surgeons tended to agree on the use of cement fixation (69%), repairing the capsule (80%), and not using a drain postoperatively (68%). Surgeons who preferentially treated hip fractures with internal fixation tended to have a lack of consensus in terms of what constituted acceptable surgical delays (43% allowing greater than 48 hours) and which screw configuration to use, with more than half using a triangle with base inferior construct. Surgeons tended to agree on the use of closed fracture reduction techniques (69%), three cannulated screws (73%), and did not routinely perform a capsulotomy (80%) or aspirate the fracture hematoma (90%). Within both treatment groups (internal fixation and arthroplasty), surgeons tended to agree on the use of perioperative antibiotics (>92%), thromboprophylaxis (98%), and postoperative weight bearing status (>87%).

Conclusions: A general lack of consensus exists among orthopedic trauma surgeons in the management of displaced femoral neck fractures. With an ever-growing emphasis upon the practice of evidence-based medicine, we have demonstrated several disparities in the technical aspects of fixation and periprosthetic care likely caused by a general lack of available evidence. We recommend the need for future research and large collaborative efforts.

Key Words: Hip fracture, Arthroplasty, Internal fixation, Outcomes.

H

ip fractures are common with approximately 280,000 cases reported each year within North America.1,2 During the next 40 years, they are expected to exceed 500,000 annually resulting in an estimated annual health care cost of at least $9.8 billion.1 They are associated with a 25% 1-year mortality rate and of those who survive, many do not return to their previous levels of function.3,4 Although there is general agreement that nondisplaced fractures require operative management of the femoral neck,5 the optimal technique for stabilization of displaced femoral neck fractures remains controversial.6,7 Operative choices for displaced femoral neck fractures include prosthetic replacement (arthroplasty) or internal fixation. These alternative implants have been compared in several observational studies and randomized trials resulting in confusion as to which method is indicated. Proponents of prosthetic replacement cite advantages of lower pain, increased mobility, and lower implant failure when compared with internal fixation.8 Surgeons disagree, however, as to whether hemiarthroplasty (unipolar or bipolar arthroplasty) versus total hip arthroplasty and cemented versus uncemented components result in better clinical outcomes.

Those in support of internal fixation report a lower risk of wound infection, reduced length of surgery, lower operative blood loss, and transfusion requirements compared with...
that of arthroplasty techniques.\textsuperscript{7,9} Despite this, there is a lack of consensus as to whether this should be accomplished using multiple screws, a single compression screw and side plate, or an intramedullary hip screw device.

The lack of concordance between cited studies may reflect differences in arthroplasty and internal fixation surgical techniques. Currently, it remains unclear whether surgeons have achieved a consensus in the technical aspects of femoral fracture fixation. We, therefore, conducted an international survey of practicing orthopedic surgeons with an interest in fracture care to clarify current opinion in issues relating to technical aspects of internal fixation and arthroplasty for patients with femoral neck fractures. We hypothesized that there was considerable variability in the techniques of operative treatment of femoral neck fractures. This survey was not intended to explore the patient-specific factors that lead surgeons toward one treatment method over another, but simply to examine the techniques they used, in general, to fix fractures or replace femoral heads in this population. Moreover, we reasoned that the results of this survey may identify those factors that influence a surgeon’s preference for a particular treatment, serve to educate the orthopedic community on issues regarding the treatment of femoral neck fractures, and assist in the planning of future clinical trials on areas that remain unresolved among orthopedic traumatologists.

**METHODS**

**Questionnaire Development**

**Item Generation**

We developed a questionnaire to examine surgeons’ preferences and practices in the management of femoral neck fractures by consulting epidemiologists and surgeons and reviewing the previous literature. Orthopedic surgeons (n = 10) in Canada and the United States participated in the development of the questionnaire. The items generated from discussion with surgeons and epidemiologists were augmented by data from a MEDLINE search of articles published from 1969 to 2003 using the text words “hip fracture”, “arthroplasty”, “internal fixation”, and “techniques”. Orthopedic traumatologists with previous publications on the topic provided additional input into potential items for the questionnaire. We employed a “sample to redundancy” strategy, contacting new surgeons until no new items for the questionnaire emerged.\textsuperscript{10}

**Pretesting and Validity Assessments**

We pretested the questionnaire with an independent group of three orthopedic surgeons and two epidemiologists to evaluate the following: (1) does the questionnaire as a whole appear to adequately address the question of current practice in treating femoral neck fractures (face validity), and (2) if the individual questions adequately reflect the domains of surgeon training and experience and surgical options for treating hip fractures (content validity).\textsuperscript{11} These surgeons also commented on the clarity and comprehensiveness of the questionnaire.\textsuperscript{11}

The final questionnaire framed the response options in one of two ways: 5-point Likert scales or nominal scales. A previous report has shown that closed-ended questions resulted in fewer incomplete questionnaires than open-ended formats.\textsuperscript{12} The respondents provided their age, gender, number of femoral neck fractures treated per year, supervision of resident trainees, continent of practice, fellowship training in trauma or hip reconstruction, and type of practice (community or academic). Academic practice was defined as a formal affiliation with a university center. Respondents expressed their preference for the technical aspects of arthroplasty and internal fixation. For arthroplasty, surgeons provided responses to the following items: (1) use of preoperative traction, (2) type of anesthesia, (3) surgical approach, (4) type of implant, (5) capsular repair, (6) use of a drain postsurgery, (7) use of perioperative antibiotics, (8) thromboprophylaxis, and (9) postoperative weight bearing. For internal fixation, surgeons responded to the following items: (1) surgical delay allowable, (2) surgical approach, (3) capsulotomy, (4) aspiration of intracapsular hematoma, (5) choice of implant, (6) screw configuration, (7) use of antibiotics, (8) thromboprophylaxis, and (9) postoperative weight bearing.

**Questionnaire Administration**

We identified all surgeons who were members of the Orthopedic Trauma Association (Active members, Associate members, International members, Senior members, Honorary members, and Emeritus members) and affiliated clinics in Europe associated with a clinical investigation unit (AO-Clinical Investigation and Documentation [AOCID, Davos, Switzerland]). Surveys were identified from the Internet-based Web sites of each organization as well as membership listings in annual meeting proceedings handbooks. Each surgeon received either a mailed package (7-page survey, a personalized cover letter, and a stamped return envelope) or an email with a link to the same survey on the Internet with an identification code. At 6 weeks, 12 weeks, and 18 weeks after the initial mailing, we remailed the questionnaire to all nonresponders. Individual responses were kept confidential and questionnaire completion was voluntary. Our local ethics review board approved the study (REB 2003-058).

**Statistical Analysis**

We summarized categorical and dichotomous variables with percentages. Continuous variables were summarized with means and standard deviations. Whenever the distribution of responses for a particular item in the questionnaire had multiple empty cells, we collapsed the categories in that particular item to achieve a more uniform distribution of responses.

**RESULTS**

**Characteristics of the Respondents**

Of the 442 surgeons who were sent the questionnaire, 298 (68%) responded. Of these, 45% responded by 6
weeks, 18% after the second mailing, 12% after the third mailing, and 18% after the fourth mailing. We received an additional 6% of responses from AO clinics to increase European surgeon input for the survey. We did not identify any significant differences in replies among the respondents at different mailing periods, suggesting those who returned the questionnaire later were not systematically different from those who responded to our initial mailing. The response rates did not differ by organization ($p = 0.32$). The typical respondent who replied to the questionnaire was in academic practice in North America (77%), aged more than 40 years (79%), and had previous orthopedic trauma fellowship training (73%). Eighty-four percent would supervise residents in a low-volume center (<100 hip fractures per year), treating less than 40 femoral neck fractures a year (70%). More than half of the surgeons reported that 30% of their patients had displaced femoral neck fractures (Table 1).

**Operative Considerations in Arthroplasty**

In elderly patients with displaced femoral neck fractures, we identified several areas of discordance among treating surgeons in terms of the type of anesthesia, surgical approach, and implants. Nineteen percent would routinely use preoperative traction, 51% preferred general anesthesia, 47% favored the posterior approach to the hip, and 50% used unipolar components (Table 2).

In contrast, we identified consensus of opinion in terms of the use of cement fixation, capsular repair, postoperative drainage, perioperative antibiotics, thromboprophylaxis, and use of preoperative traction. Even though surgeons varied in the types of components used, more than two-thirds (69%) used cement for fixation. In addition, 80% repaired the capsule and 68% did not leave a postoperative drain. Ninety-nine percent of surgeons gave perioperative antibiotics and continued them for a duration of 1 day to 2 days (94%). Ninety-eight percent used some form of deep venous thrombosis (DVT) prophylaxis within their patients; 63% used chemical prophylaxis, of which low molecular weight heparin was the most common (47%), and 53% used compression devices. The majority of surgeons (99%) allowed partial (19%) or full (80%) weight bearing postoperatively (Table 2).

**Operative Considerations in Internal Fixation**

We found there was a significant lack of concordance with respect to surgical timing for patients whose displaced femoral fractures were treated by internal fixation (Table 3). Forty-seven percent of surgeons tolerated a surgical delay of more than 36 hours, of which 43% would allow more than 48 hours before taking the patient to the operating room. Among those surgeons who preferred a triangle screw configuration, more than half used a triangle with base inferior construct (51%), with the remainder using a triangle with base superior positioning.

Respondents tended to agree upon the surgical approach, the need for capsulotomy and aspirating the fracture hematoma, implant choice, and postoperative management. Sixty-nine percent advocated the use of closed reduction techniques with 86% using screw fixation to hold the fracture. Of those using screw fixation, 79% preferred cannulated screws with 73% using a three-screw construct. The majority of surgeons did not routinely perform a capsulotomy (80%) or aspirate the fracture hematoma (90%). Postoperatively, 94% used antibiotics for up to 2 days, 98% gave DVT prophylaxis, and 87% permitted

---

**Table 1** Characteristics of Respondents ($N = 298$)

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (%) (yr)</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;30</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>31–40</td>
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<td>20</td>
</tr>
<tr>
<td>41–50</td>
<td>134</td>
<td>45</td>
</tr>
<tr>
<td>51–60</td>
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<td>26</td>
</tr>
<tr>
<td>&gt;60</td>
<td>24</td>
<td>8</td>
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<tr>
<td><strong>No. (%) yr in practice</strong></td>
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<tr>
<td>&lt;5</td>
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<td></td>
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<tr>
<td>5–10</td>
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<td>11–15</td>
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<td>16–20</td>
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<td>18</td>
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<td>&gt;20</td>
<td>90</td>
<td>31</td>
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<tr>
<td><strong>Type of work setting (%)</strong></td>
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<tr>
<td>Academic</td>
<td>228</td>
<td>76</td>
</tr>
<tr>
<td>Nonacademic</td>
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<td>24</td>
</tr>
<tr>
<td><strong>Continent of practice (%)</strong></td>
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<td></td>
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<td>77</td>
</tr>
<tr>
<td>Europe</td>
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<td>21</td>
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<tr>
<td><strong>Supervise residents in training (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>84</td>
</tr>
<tr>
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<tr>
<td><strong>Fellowship training (%)</strong></td>
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<td></td>
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<tr>
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<tr>
<td>No</td>
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<tr>
<td><strong>Fellowship in adult joint reconstruction (%)</strong></td>
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<td><strong>No. femoral neck fractures treated</strong></td>
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<tr>
<td>per year (personal series)</td>
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<td>&lt;40</td>
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<td>≥40</td>
<td>89</td>
<td>30</td>
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<tr>
<td><strong>No. femoral neck fractures treated</strong></td>
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<td></td>
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<tr>
<td>at institution per year</td>
<td></td>
<td></td>
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<td>&lt;100</td>
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<td>16</td>
</tr>
<tr>
<td><strong>Proportion of displaced:</strong></td>
<td></td>
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</tr>
<tr>
<td>undisplaced fractures that are treated at institution per year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 displaced</td>
<td>153</td>
<td>51</td>
</tr>
<tr>
<td>≥30% displaced</td>
<td>145</td>
<td>49</td>
</tr>
</tbody>
</table>
patients to weight bear (40% full and 47% partial weight bearing) (Table 2).

**DISCUSSION**

Our survey identified considerable discordance among surgeons in their preferences for arthroplasty and internal fixation. The choice of treatment method for displaced femoral neck fractures, however, remains controversial as borne out by the myriad of conflicting clinical reports within the literature.

Although this survey demonstrated some elements of agreement, there were several areas of disparity among the orthopedic surgeons, 73% of whom had completed an orthopedic trauma fellowship, in terms of technical aspects of fixation of displaced femoral neck fractures. Discrepancies among surgeons may have reflected the differing perceptions. Previous studies have been limited by their small sample sizes, incomplete assessment of possible confounding variables, and wide confidence intervals surrounding the treatment effects.

The strengths of our study include (1) a rigorous process of development of the questionnaire items with active surgeon participation; (2) a comprehensive sampling of surgeons

---

**Table 2 Technical Aspects of Arthroplasty Among 298 Trauma Surgeons**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative traction</td>
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</tr>
<tr>
<td>Always</td>
<td>19</td>
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<td>Sometimes</td>
<td>36</td>
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<tr>
<td>Never</td>
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<td>Anesthesia</td>
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<td>Surgical approach</td>
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<tr>
<td>Lateral</td>
<td>24</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>28</td>
</tr>
<tr>
<td>Posterior</td>
<td>47</td>
</tr>
<tr>
<td>Implant</td>
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</tr>
<tr>
<td>Unipolar arthroplasty</td>
<td></td>
</tr>
<tr>
<td>Uncemented</td>
<td>14</td>
</tr>
<tr>
<td>Cemented</td>
<td>36</td>
</tr>
<tr>
<td>Bipolar arthroplasty</td>
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</tr>
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<td>Uncemented</td>
<td>11</td>
</tr>
<tr>
<td>Cemented</td>
<td>29</td>
</tr>
<tr>
<td>Total hip arthroplasty</td>
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<td>Uncemented</td>
<td>6</td>
</tr>
<tr>
<td>Cemented</td>
<td>4</td>
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<tr>
<td>Capsular repair (%)</td>
<td>80</td>
</tr>
<tr>
<td>Drain postoperatively (%)</td>
<td>32</td>
</tr>
<tr>
<td>Perioperative antibiotics (%)</td>
<td>99</td>
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<tr>
<td>Duration of antibiotics</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
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<td>3</td>
<td>5</td>
</tr>
<tr>
<td>&gt;3 d</td>
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<tr>
<td>DVT prophylaxis (%)</td>
<td>98</td>
</tr>
<tr>
<td>Heparin</td>
<td>17</td>
</tr>
<tr>
<td>LMWH</td>
<td>88</td>
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<tr>
<td>Warfarin</td>
<td>46</td>
</tr>
<tr>
<td>Aspirin</td>
<td>38</td>
</tr>
<tr>
<td>Compression stocking</td>
<td>78</td>
</tr>
<tr>
<td>Pneumatic compression devices</td>
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<tr>
<td>Postoperative weight bearing</td>
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</tr>
<tr>
<td>No</td>
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</tr>
<tr>
<td>Partial</td>
<td>19</td>
</tr>
<tr>
<td>Full</td>
<td>80</td>
</tr>
</tbody>
</table>

LMWH, low molecular weight heparin.

**Table 3 Technical Aspects for Displaced Femoral Neck Fracture Internal Fixation Among 298 Trauma Surgeons**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>Surgical delay allowable</td>
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<tr>
<td>&lt;6 h</td>
<td>5</td>
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<tr>
<td>6–12 h</td>
<td>10</td>
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<tr>
<td>13–24 h</td>
<td>18</td>
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<tr>
<td>24–36 h</td>
<td>20</td>
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<tr>
<td>37–48 h</td>
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<td>&gt;48 h</td>
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<tr>
<td>Surgical approach</td>
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<td>Closed reduction</td>
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<td>Open reduction</td>
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<td>Anterior</td>
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<tr>
<td>Anterolateral</td>
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<tr>
<td>Posterior</td>
<td>11</td>
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<tr>
<td>Capsulotomy</td>
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<td>Aspirate hematoma</td>
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<tr>
<td>Implant choice</td>
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<td>Compression screw and side plate</td>
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<tr>
<td>Intramedullary hip screw</td>
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<tr>
<td>Cannulated screws</td>
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<td>2 Screws</td>
<td>3</td>
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<tr>
<td>3 Screws</td>
<td>73</td>
</tr>
<tr>
<td>4 Screws</td>
<td>3</td>
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<tr>
<td>Noncannulated screws</td>
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<tr>
<td>Triangle with base superior</td>
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<td>Postoperative weight bearing</td>
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<tr>
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<tr>
<td>DVT prophylaxis (%)</td>
<td>98</td>
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</tr>
<tr>
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<td>80</td>
</tr>
</tbody>
</table>

LMWH, low molecular weight heparin.

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with an interest in caring for trauma patients; and (3) lack of response bias among later responders. Our response rate is acceptable (68%) but could be higher, thus limiting the extent of nonresponder bias.13,14 The results may not, however, be generalizable to orthopedic surgeons who are not members of the Orthopedic Trauma Association or AO-affiliated centers in Europe. Given that the Orthopedic Trauma Association membership is heavily based in North America, our results also may not reflect the preferences of the surgeons working in nonacademic centers and in other continents. Although we collected data on surgical delay, our findings are limited by a lack of understanding of why surgeons perceive their patients were delayed to surgery. This survey aimed primarily to identify what specific technical considerations were involved when a surgeon decided to treat a patient with one type of implant, regardless of the rationale for doing so. Thus, our findings do not shed light on the factors (patient-specific) that are involved in the decision-making process between choosing arthroplasty or internal fixation for a particular femoral neck fracture.

There is a paucity of evidence for the use of preoperative traction, with more than half the number of surgeons within the arthroplasty group using it during their care of hip fracture patients.15-17 In addition, more than 50% used general anesthesia in their practice despite reports advocating the use of regional techniques in most patients owing to reduced short-term mortality rates, decreased incidence of deep venous thrombosis, and lower incidence of myocardial infarction.18-20

Hip fractures are associated with increased mortality among elderly patients resulting in many advocating expedited surgery within 24 hours.21,22 Others have stated that a delay of no greater than 4 days is acceptable, especially in patients with associated medical comorbidities requiring preoperative optimization.23 This variation in surgical timing is borne out by our findings that more than two-thirds of surgeons accepted surgical delays of more than 24 hours. This discordance may be related to surgeons adopting principles from the large number of observational reports rather than from prospective randomized trials.21,22

Surgeon differences regarding optimal approaches to fix displaced femoral neck fractures also parallel current lack of evidence. In a meta-analysis involving nearly 5,000 patients, Parker and Blundell24 found no significant differences between alternative implants. Despite lower revision rates in patients treated with prosthetic head replacement (0%-24% compared with 10%-48.8% with internal fixation), arthroplasty resulted in significantly increased risk of infection \( p = 0.009 \), greater blood loss \( p < 0.05 \), and longer surgical times \( p < 0.05 \).25

Surgeons disagreed on the type of prosthesis for arthroplasty. Unipolar arthroplasty was used in 50% of cases compared with bipolar arthroplasty in 40%, and total hip replacements in 10% of cases. This finding parallels a current lack of evidence regarding the decision to use a total hip arthroplasty versus hemiarthroplasty.25,26 Although the potential advantages of total hip arthroplasty include improved function and decreased pain compared with hemiarthroplasty, the higher dislocation rates with total hip arthroplasty remains an important trade off.

A previous meta-analysis24 demonstrated that compression screw and side plate fixation yielded more favorable results in terms of fewer fracture healing complications compared with fixation with three or more screws. Despite this evidence, only 11% of surgeons in this study used compression screw and side plate techniques compared with the majority (86%) who used screw only constructs. Of those preferring screw only fixation, 49% used a triangle with apex screw superior compared with 51% who inserted the apex screw in an inferior position. A study by Selvan et al.27 demonstrated that an inverted triangular screw construct was biomechanically superior to alternative configurations. However, persuasive clinical data are lacking.

Although this survey did identify several areas of discordance in the management of femoral neck fractures, surgeons did agree in several areas. For arthroplasty, more than two-thirds of surgeons used cement fixation for their components. This mode of practice is in keeping with studies that have shown lower rates of revision with cemented hemiarthroplasty prostheses and evidence of better functional outcome and lower rates of thigh pain when cement is used.28-31 This, however, needs to be balanced by reports suggesting that cementing may be associated with a higher mortality or greater difficulty should revision be required.32-34

General consensus was achieved in regard to the management of hip fracture patients postoperatively in terms of antibiotic use, thromboprophylaxis, and weight bearing regimes. Although 99% of surgeons prescribed perioperative antibiotics after hip arthroplasty, almost half (48%) continued them for longer than 24 hours after surgery. This practice is not in keeping with evidence-based guidelines35 as a recent meta-analysis by Southwell-Keely et al.36 highlighted that there was no difference in terms of prophylaxis between one dose versus several doses of antibiotics.

In conclusion, this study serves to highlight the lack of agreement among surgeons in the management of displaced femoral neck fractures. This can most likely be attributed to varying inferences drawn from a range of invalidated clinical studies that use different operative procedures and employ several outcome measures. Deciding when evidence is sufficient to conclude that one management approach is superior to another is a subjective matter, and inevitably somewhat arbitrary. In addition, surgeon decision making is far more complex than the identifying “evidence” in favor of one implant over another. The choice of implant may be more related to inventory-driven, rather than patient-driven, factors. Another key tenet of evidence-based medicine focuses upon understanding the local circumstances of practice (i.e., budgets and costs of implants).
Within the published literature to date, there is no definitive evidence establishing the optimal method of fixation for displaced femoral neck fractures. This lack of evidence is reflected in the variability of surgeons’ views and preferences. Given that the number of patients presenting with this problem is only set to increase, it is our belief that further research is warranted to establish a uniform set of guidelines for the management of this condition.

Ultimately, the discordant perceptions and lack of high quality clinical evidence supports the need for large randomized trials evaluating the optimal internal fixation device and trials examining the optimal type of arthroplasty in patients with displaced femoral neck fractures.

REFERENCES


Resorbable Fillers Reduce Stress Risers From Empty Screw Holes

J. Winslow Alford, MD, Michael P. Bradley, MD, MS, Paul D. Fadale, MD, Joseph J. Crisco, PhD, Douglas C. Moore, MS, and Michael G. Ehrlich, MD

Background: Empty screw holes after hardware removal are stress risers that weaken bone and can lead to refracture in an active individual. We sought to reduce these stress risers. We hypothesize that resorbable screws used as hole fillers would (1) provide immediate strength and (2) maintain this strength during resorption.

Methods: Randomized, prospective controlled animal laboratory study with 75 live New Zealand white rabbits’ paired femurs. Single mid-diaphyseal holes were filled with a metal or resorbable screw; contralateral femurs were paired empty hole controls. Main outcome measures included histologic analysis, torsion to failure, peak torque, energy to failure, and stiffness at baseline, 1 week, and 13 weeks postimplantation.

Results: At time baseline, resorbable fillers produced an immediate 30% increase in the peak torque ($p = 0.01$) and 73% increase in peak energy ($p = 0.006$). Metal screws produced a 17% increase in peak torque ($p = 0.038$), and a 58% increase in the amount of energy to failure ($p = 0.009$). At 1 week, although the resorbable ($p = 0.01$) but not the metal ($p = 0.82$) screws increased the peak torque, both metal ($p = 0.003$) and resorbable ($p = 0.050$) screws increased the peak energy compared with contralateral empty controls. At 13 weeks, metal and resorbable screw-filled bones were as strong as the healed contralateral femurs. Partial screw resorption and new bone formation without lysis was demonstrated histologically. Resorbable screw hole fillers immediately increase the strength of bones without weakening during early resorption.

Conclusions: Placing resorbable fillers in bone defects after hardware removal could reduce the likelihood of refracture.

Key Words: Stress riser, Filler, Resorbable, Screw hole, Refracture.


Although plates and screws are generally left in place after a fracture has healed, retained hardware has been associated with complications, especially in active athletic individuals. Hardware removal, however, involves surgical risks and produces stress risers, which may lead to refracture. Often these patients require mechanical protection after hardware removal.

Currently, implanted hardware is left in place until it causes a specific problem, but asymptomatic hardware has been associated with severe consequences, particularly in high demand patients. In a 10-year review of National Football League players, there was a 17% refracture rate in football players with well-healed fractures and asymptomatic plates. In this series, the average time to internal fixation was 1.5 days after injury, and all fractures were internally fixed using standard plating techniques without intraoperative complications. The average time to player reactivation was 18 weeks after surgery, but even with these cautious methods, 17% of the players sustained refracture after reactivation.1 A similar survey of Rugby players in England from 1990 to 1997 revealed a considerable complication rate in players with retained hardware. After fracture fixation, the players resumed their preinjury level of participation within 1 month to 12 months. In this series, 13% of these athletes suffered complications in relation to the retained implant.2 A refracture or other inactivating complication in an athlete or laborer causes a considerable professional, socioeconomic, and psychological loss.3

Routine removal of asymptomatic plates as a method of avoiding these complications may be a more risky policy than leaving them in, however. Besides exposing the patient to the surgical risk, even successfully removed hardware causes localized microtrauma to the bone and leaves behind empty screw holes, which act as stress risers. The combination of the removal process and the residual empty holes weaken bone and place the patient at risk for refracture. To prevent refracture after plate removal, the athlete or high demand patient today must endure a prolonged period of mechanical protection before his or her full reactivation. The duration of this protected period is of some debate, but recommendations range from several weeks4–7 to a full year.8 The cost of this inactivation to an active individual is substantial.

Despite risks involved with hardware removal, it is performed routinely,9 and for decades, the stress concentration resulting from bone defects after hardware removal has presented a challenge to the orthopedic community. Rates of refracture after hardware removal range from 7% to 26% depending on hardware type and location, with higher rates seen in the forearm after the removal of larger plates, partic-
ularly from young and athletic patients.\textsuperscript{2,6,10–13} The weakening effect of plates and screws is a combination of localized osteopenia from plate-induced ischemia,\textsuperscript{14} microtrauma at the screw-bone interface, and stress risers from empty screw holes. Although extreme osteopenia will weaken bone,\textsuperscript{15} studies indicate that until bone is demineralized by 75\%, there is no significant weakening in torsion.\textsuperscript{16} Even an uncomplicated screw removal process is thought to cause microtrauma in the surrounding bone as the screw is loosened, but unless a large amount of bone is removed, this represents a minor percentage of the overall weakening effect. With respect to screw holes, however, it has been shown that a bicortical hole representing only 20\% of the diameter of the cortex resulted in up to 50\% reduction in torsional peak load to failure.\textsuperscript{17,18} This corresponds to a 3.5-mm screw hole in a 1.7-cm radius, ulna, or fibula. Thus, it is clear that the residual screw holes are a major weakening feature of a bone after hardware removal.

To date, no intervention has successfully reduced stress risers immediately after hardware removal\textsuperscript{19–21} and maintained initial strength during a healing period.\textsuperscript{22} Previous efforts to augment bone strength by accelerating screw hole filling have not been successful. In 1970, Brooks et al.\textsuperscript{17} attempted to increase the rate of new bone formation in screw holes by over drilling screw holes after screw removal. They hoped to accelerate the healing process and stimulate bone formation by causing localized bleeding and removing the fibrous tissue that forms in the screw-bone interface. In their study, woven bone filled both drilled and undrilled holes at equal rates, and they were unable to demonstrate increased mechanical strength in the bones with redrilled screw holes. Attempts at bone grafting screw holes in living dogs met with similar disappointment.\textsuperscript{20,21} Although bone grafting possibly increased bone quantity in screw holes, there was no evidence that additional bone lead to an increase in whole bone strength.

Calcium phosphate cement injected into unicortical defects in rabbit femurs provided immediate strength to rabbit femurs in vivo, but the intramedullary expansion of the cement seemed to hamper healing and new bone formation, presumably caused by disruption of the intramedullary blood supply, which caused the filled bone to remain weaker than an intact bone, even 3 months after injection.\textsuperscript{22}

Our goal in this study was to develop a method that would strengthen bones immediately after hardware removal without weakening the bone during the healing process. Because fractures usually occur shortly after hardware removal,\textsuperscript{10,12} any method of reducing stress risers and strengthening bone must satisfy two objectives: (1) provide immediate strength at the time of implantation, and (2) preserve strength during bone replacement. We chose both a permanent metal screw, which would provide immediate strength, as our standard control versus a resorbable screw, which has the theoretic benefits of resorption over time. Also, our resorbable screw would act as a filler, but not theoretically have the detrimental effects of calcium phosphate cement, which may cause expansion and intramedullary blood supply disruption. To our knowledge, although different composition of screws exists, no clinical differences exist between resorbable screws despite resorption time differences. The hypothesis of this study is that the filling of empty bicortical diaphyseal bone holes with screw fillers would improve immediate and long-term effects on bone strength.

**MATERIALS AND METHODS**

The effect of screw hole filling was tested using paired femurs from 75 rabbits. For each pair, one was filled with either a metal or resorbable bone screw, and the other left empty. The predictable size and growth patterns of the New Zealand white rabbit make it a suitable animal for our model, and it has been commonly used in prior studies.\textsuperscript{17,23} Six-month-old rabbits were chosen for their active bone physiology and the appropriate size of their femurs relative to the size of the implants used.\textsuperscript{22}

After approval from our Animal Welfare Committee, 75 female New Zealand white rabbits were assigned to three groups to determine the time of bone harvest at time 0, 1 week, and 13 weeks. Time 0 rabbits (n = 15) were killed at the time of screw placement. The remaining rabbits were placed under general anesthesia for surgery and killed at 1 week (n = 30) and 13 weeks (n = 30) postimplantation.

At screw placement, the rabbits were further randomized to receive either a standard 2-mm AO stainless steel screw (Synthes, Paoli, PA), “metal”, or a 2-mm resorbable screw (82\% polylactic acid and 18\% polyglycolic acid [PGA], Biomet, Inc., Warsaw, IN), “resorbable”. Thread pitch and insertion methods were identical. The metal group was used for comparison with the current familiar clinical scenario of bones filled with metal screws; currently, holes are left empty after removal of metal screws. A single midshaft bicortical hole was drilled in the anteroposterior direction through right and left femurs. The holes were 2 mm in diameter, which was approximately 20\% of the overall midshaft diameter. Before screw insertion, the holes were tapped using the specified manufacturer-supplied tap. The screws were inserted through both cortices. The empty holes in the contralateral control bones were also tapped to match the holes in the filled bones.

The rabbits were individually caged and permitted unrestricted motion and weightbearing throughout the postoperative period. They were monitored regularly for signs of infection, fracture, or irregular behaviors, which could indicate other pathophysiologic problems.

Upon harvesting, the femurs were carefully cleaned of the muscle and fascia, and the proximal and distal epiphyses were removed. To prepare the specimens for potting, 1.0-mm crossed k-wires were placed 5 mm from the proximal and distal physis, and the bone ends were potted with polymethylmethacrylate in square aluminum (2.54 cm) tube stock. During potting, care was taken to preserve a constant 45-mm gauge length of free bone between the potting surfaces. When not being potted or tested, the bones were wrapped in saline-
Mechanical testing of the paired bones was accomplished by applying a torque in external rotation using a servohydraulic torsional testing machine (Model 8521s, Instron Corporation, Canton, MA). The bones were torqued at a constant rate of 10 degrees per second, and torque-rotation data were recorded at 200 Hz with a digital data acquisition system. Torque versus rotation data were reduced to determine the peak torque, total energy to failure, and stiffness of the specimen. The peak torque was defined to be the maximum value of the torque-rotation curve to the point of failure. The total energy was determined by integrating the torque-rotation curve to the point of failure. The stiffness was determined by measuring the slope of the linear portion of the torque-rotation curve after exclusion of the toe region using custom-designed LabView software (National Instruments, Austin, TX). The paired data were analyzed by Student t test with Instat software (Graphpad Software, Inc., San Diego, CA) on a personal computer. The values on the filled side were expressed as a percentage increase over the paired empty bone, which facilitated comparison between young rabbits’ bones at small forces and older rabbits’ bones at larger forces.

At the conclusion of testing, the fracture pattern of each bone was also assessed. Notation was made of the fracture type (spiral, transverse, or comminuted), as well as the angle bone was also assessed. Notation was made of the fracture pattern of each bone. In addition, we noted whether type (spiral, transverse, or comminuted), as well as the angle of the fracture relative to the long axis of the bone (measured with a miniature goniometer). In addition, we noted whether the fracture passed through none, one, or both of the two cortical defects created by a single bicortical screw hole and these data were analyzed using \( \chi^2 \) in Instat software (Graphpad Software, Inc.).

Eight randomly selected rabbits from 1 week \( (n = 2) \) and 13 weeks \( (n = 6) \) were harvested in an identical manner, and their femora were set aside for histologic analysis. These bones were decalcified in a modified Richman-Gellfand Hill solution (10% HCl, 12.5% formic acid, and 3% floresculcinol) for 12 days, embedded in paraffin, and histologic slides were stained in hematoxylin and eosin and Safranin O. These slides were used for qualitative analysis of the bone replacement process. A power analysis was performed to assure statistical validity.

RESULTS

Of the 75 rabbits entered into the study, there were 11 unexpected exclusions, resulting in 64 rabbits available for data collection (mechanical testing or histology) at time 0 \( (n = 12) \), 1 week \( (n = 24) \), and 13 weeks \( (n = 20) \) postimplantation. The exclusions were because two rabbits that were killed early (one because of self-mutilation and the other because of a spine fracture resulting in paralysis). An additional nine rabbits were excluded because they fractured their femurs before data collection: eight in vivo and one during specimen preparation \( (\text{time 0 group}) \). In each case, it was the empty femur, not its paired filled femur that fractured. The distribution of those unexpected fractures was one in the metal 1-week group, one in the metal 13-week group, one in the resorbable 0 week group, four in the resorbable 1-week group, and two in the resorbable 13-week group. It is unclear when the fractures in the 13-week group occurred, as they were partially healed at harvest. After these 11 rabbits were eliminated, 64 rabbits remained for data collection. Of these, eight rabbits were randomly selected for histologic analysis: two were from the resorbable 1-week group, three were from the resorbable 13-week group, and three were from the metal 13-week group, resulting in a total of 56 rabbits available for mechanical testing.

Mechanical Properties Testing

At time 0, filling the empty hole with resorbable fillers immediately produced a mean increase of 23% in the torque to failure \( (p = 0.01) \) and a 73% increase in the amount of energy to failure \( (p = 0.006) \). The metal fillers also increased the peak torque and energy to failure, but less than the resorbable fillers did. A metal filler immediately produced a mean 17% increase in maximum torque to failure over its paired empty hole bone \( (p = 0.038) \), and a 58% increase in the amount of energy to failure \( (p = 0.009) \). At time 0, there was no difference in stiffness of the empty bones and bones filled with either metal or resorbable fillers (Fig. 1).

There was a general increase in strength of filled and empty femurs in all groups as the rabbits grew (Table 1). At 1 week, the femurs that had their holes filled with resorbable fillers showed a greater peak torque than their empty pairs did \( (2.88 \text{ Nm} \pm 0.55 \text{ Nm} \text{ vs. } 2.48 \text{ Nm} \pm 0.5 \text{ Nm}, p = 0.01) \), with no significant difference at 13 weeks \( (6.63 \text{ Nm} \pm 0.84 \text{ Nm} \text{ vs. } 6.51 \text{ Nm} \pm 0.8 \text{ Nm}, p = 0.41) \). Likewise, the energy absorption to failure also trended higher for the resorbable-filled bones than for their empty pairs \( (12.95 \text{ Nm} \pm 5.23 \text{ Nm} \text{ vs. } 11.53 \text{ Nm} \pm 3.57 \text{ Nm} \cdot \text{deg} p = 0.0501) \) at 1 week, with no significantly different at 13 weeks \( (43.68 \text{ Nm} \pm 7.07 \text{ Nm} \text{ vs. } 46.12 \text{ Nm} \pm 8.38 \text{ Nm} \cdot \text{deg}, p = 0.08) \). In contrast to the resorbable group, the metal-filled bones demonstrated no difference when compared with their empty pairs in torsional load at 1 week \( (3.54 \text{ Nm} \pm 0.92 \text{ Nm} \text{ vs. } 3.47 \text{ Nm} \pm 0.86 \text{ Nm}, p = 0.82) \). They did, however, demonstrate a higher energy to failure \( (18.42 \text{ Nm} \pm 8.31 \text{ Nm} \text{ vs. } 11.49 \text{ Nm} \pm 2.79 \text{ Nm} \cdot \text{deg}, p = 0.03) \) at 1 week, and no difference in peak torque \( (6.82 \text{ Nm} \pm 0.75 \text{ Nm} \text{ vs. } 6.4 \text{ Nm} \pm 1.75 \text{ Nm}, p = 0.23) \) or energy \( (41.8 \text{ Nm} \pm 16.79 \text{ Nm} \text{ vs. } 44.55 \text{ Nm} \pm 6.39 \text{ Nm} \cdot \text{deg}, p = 0.64) \) at 13 weeks. There was no change in the stiffness of metal or resorbable-filled bones throughout the experiment.

Bone and Fracture Characteristics

Upon gross inspection of the specimens at 1 week and 13 weeks, the empty drill hole in the control femoral shafts became progressively smaller over time as new bone formed. Thirteen weeks postoperatively, the hole was only occasionally visible as a tiny dimple in the empty hole specimens. The
heads of resorbable screws were partially dissolved at 13 weeks, and several were covered with bone. In contrast, all the metal screw heads and tips were plainly visible. Histologically, the empty screw holes filled in with normal appearing woven bone, with partial reconstitution of the cortex at 13 weeks. Predictably, the bone surrounding the metal-filled holes showed very little histologic change, with a distinct outline of the screw threads visible at 13 weeks. In contrast, the resorbable screws demonstrated the early phases of implant degradation and resorption, with gradual new bone formation and partial cortex reconstitution at 13 weeks (Fig. 2). There was no evidence of bone lysis or inflammatory reaction during this resorption process.

The fractures in specimens from the early groups (time 0 and 1 week) occurred in a spiral pattern at a 45-degree angle (±2 degrees) to the long axis of the bone. A single bicortical hole creates two cortical defects; if a hole was filled with a resorbable screw, the fracture was more likely to miss one of the two defects than it was in the group with metal-filled holes (Fig. 3). In the early groups (time 0 and 1 week), the fractures of only 3 of 14 resorbable-filled bones passed through both cortical defects, whereas the fractures in 9 of 14 of their contralateral empty pairs passed through both cortical defects. This difference in the resorbable group was statistically significant by $\chi^2 (\chi^2 = 0.02)$. For the metal groups, fractures passed through both cortical defects in 7 of 22 filled

![Resorbable Filler Percentage Change](https://example.com/resorbable-graph.png)

**Fig. 1.** Graphs depicting percentage change of torque (Nm), energy (Nm ° deg), and stiffness (Nm/deg) for metal- and resorbable-filled femurs compared with their paired empty hole femurs at time 0, 1 week, and 13 weeks. *p ≤ 0.05.

| Table 1 | Torque (Nm), Energy (Nm ° deg), and Stiffness (Nm/deg) for Metal and Resorbable-Filled Bones Compared With Their Paired Empty Hole Bones at Time 0, 1 wk, and 13 wk |
|---------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Torque  | Energy                                                                                        | Stiffness                                                                                        |
| Nm      | Change (%)                                                                                     | Nm ° deg                                                                                         | Change (%)                                                                                     | p       |
| Empty   |                                                                                               |                                                                                                 |                                                                                                 |         |
| Time 0  |                                                                                               |                                                                                                 |                                                                                                 |         |
| Empty, n = 6 | 1.44 ± 0.18 22.9 0.011                                                                           | 3.38 ± 0.81 73.4 0.006                                                                            | 0.35 ± 0.05 –11.4 0.053                                                                         |         |
| Filled, n = 6 | 1.77 ± 0.33                                                                                  | 5.86 ± 1.71                                                                                     | 0.31 ± 0.06                                                                                     |         |
| 1 wk    |                                                                                               |                                                                                                 |                                                                                                 |         |
| Empty, n = 8 | 2.48 ± 0.59 16.1 0.01                                                                            | 11.53 ± 3.57 12.3 0.050                                                                           | 0.32 ± 0.073 6.2 0.31                                                                           |         |
| Filled, n = 8 | 2.88 ± 0.55                                                                                  | 12.95 ± 5.23                                                                                     | 0.34 ± 0.073 6.2 0.31                                                                           |         |
| 13 wk   |                                                                                               |                                                                                                 |                                                                                                 |         |
| Empty, n = 10 | 6.63 ± 0.84 –1.8 0.41                                                                            | 46.12 ± 8.38 –5.3 0.085                                                                           | 0.5 ± 0.071 0 0.62                                                                            |         |
| Filled, n = 10 | 6.51 ± 0.66                                                                                  | 43.68 ± 7.07                                                                                     | 0.5 ± 0.06                                                                                     |         |
| Metal   |                                                                                               |                                                                                                 |                                                                                                 |         |
| Time 0  |                                                                                               |                                                                                                 |                                                                                                 |         |
| Empty, n = 6 | 1.68 ± 0.47 17.2 0.038                                                                           | 5.66 ± 2.18 58 0.009                                                                             | 0.24 ± 0.07 20.8 0.3                                                                            |         |
| Filled, n = 6 | 1.97 ± 0.38                                                                                  | 8.97 ± 2.72                                                                                     | 0.29 ± 0.05                                                                                     |         |
| 1 wk    |                                                                                               |                                                                                                 |                                                                                                 |         |
| Empty, n = 16 | 3.47 ± 0.86 2 0.823                                                                           | 11.49 ± 2.79 60.3 0.003                                                                           | 0.34 ± 0.035 2.9 0.67                                                                            |         |
| Filled, n = 16 | 3.54 ± 0.92                                                                                  | 18.42 ± 8.31                                                                                     | 0.35 ± 0.055 2.9 0.67                                                                            |         |
| 13 wk   |                                                                                               |                                                                                                 |                                                                                                 |         |
| Empty, n = 10 | 6.4 ± 1.75 6.5 0.23                                                                            | 41.8 ± 16.79 6.5 0.642                                                                           | 0.52 ± 0.07 3.8 0.74                                                                            |         |
| Filled, n = 10 | 6.82 ± 0.75                                                                                  | 44.55 ± 6.39                                                                                     | 0.54 ± 0.092                                                                                   |         |
bones and 9 of 22 of their paired empty bones, which was not statistically different by $\chi^2 (\chi_0^2 = 0.33)$. At 13 weeks, both metal and resorbable-filled bones, as well as their healed empty pairs, produced a comminuted pattern, with no single discernable fracture line (Fig. 3).

**DISCUSSION**

The weakening effect of stress risers after hardware removal continues to challenge the orthopedic community. In this study, we sought to reduce the stress riser effect of an empty screw hole by filling it with a resorbable filler. Our mechanical data demonstrate an immediate strength increase without weakening during implant resorption.

Refracture is primarily a concern in young high-demand patients, but in the Medicare population alone, roughly 500,000 patients per year sustain fractures requiring the care of an orthopedic surgeon. Rates of surgical treatment of these fractures involving hardware implantation vary geographically and with fracture type but are as high as 77.1% in the ankle and 65.2% in the forearm. A reported associated hardware removal rate of 23% in the ankle, for example, means that problems associated with removal of orthopedic hardware are of concern for all practicing orthopedic surgeons worldwide. Rates of surgical treatment and subsequent hardware removal are likely to be even higher in a high-demand patient population.

The current gold standard for orthopedic hardware removal is to leave screw holes empty after hardware removal. Therefore, the comparison between an empty hole and its paired resorbable-filled bone is of key importance. Reminger et al. showed that a bicortical screw was stronger than an empty bicortical hole; however, both were weaker than intact bone. Our data demonstrate an immediate strengthening effect of filling screw holes with resorbable screws, with no evidence of lysis or weakening as they are replaced by bone. Resorbable-filled bones were immediately able to withstand a higher load and absorb more energy before fracture than are their matched empty femurs at both time 0 and 1 week. There was no significant weakening effect during implant resorption and bone replacement. At 13 weeks, the ultimate torsional load, energy absorption to failure, and torsional stiffness of the metal and resorbable screw-filled bones were as strong as the healed bones, which had been left to fill in naturally. These values were comparable to those of intact femurs.

It is noted that of the unexpected fractures of empty (control) femurs, a significantly higher number of the resorbable empty femurs than the metal femurs fractured unexpectedly. This is likely caused by the fact that the different screw systems required the use of slightly different taps, and we conclude that the resorbable tap system was more damaging than the metal screw tap was. This means that the protective effect of the resorbable screw fillers was demonstrated in the face of a weaker bone construct than the metal screws were. It suggests that the resorbable screw fillers have an ability to strengthen bones, which have been weakened from the microtrauma associated with screw removal.

Of additional interest is the fact that the increase in peak load of the resorbable-filled bones is greater than the peak load increase in the metal-filled bones at time 0 and 1 week. Although metal screws demonstrated a higher increase in energy to failure than the resorbable screws did at 1 week, the greater increase in peak load for the resorbable group is intriguing. The metal-filled bones represent the condition of a bone before screw removal and their controls were likely tapped by a less damaging instrument, which explains why they demonstrated a higher energy to failure at 1 week. In a clinical setting, these findings suggest that changing a metal screw with a resorbable screw may result in a construct that can withstand higher torsional loads.

Our findings support our hypothesis that filling an empty screw hole with a resorbable screw can immediately reduce its stress riser effect. Clinical studies indicate that refracture usually occurs shortly after plate removal and animal studies demonstrate early screw hole filling and increased
strength just 4 weeks after screw removal. Therefore, we propose that an immediate increase in maximum load to failure and energy absorbing capacity could raise the threshold for refracture in active patients during this early risky period after hardware removal. The fact that these fillers had no weakening effect during the early phases of resorption and new bone formation is particularly encouraging, because of the concerns of bone lysis or loosening during polymer resorption.

Degradation of the most commonly used synthetic bio-degradable polymers, poly-(l-lactide) and polyglycolide (PGA) begins with hydrolysis as the implant absorbs water. The resulting fragments are phagocytosed by macrophages and polymorphonuclear leukocytes, and lactic acid polymers are reduced and dissimilated via the Krebs Cycle. Regional lactic acid overload could lead to prostaglandin release and osteolysis. The likelihood of this problem occurring is determined by polymer type, implant size, and the rate of implant degradation, which is determined by the material’s crystallinity. Highly crystalline poly-(l-lactide) implants persist 20 months after implantation and have entered lymphatic systems in sheep. More rapid breakdown seen with PGA implants is associated with sterile abscesses and osteolysis.

Fig. 3. Fracture lines were more likely to miss holes filled with resorbable fillers. At 3 months, the fracture pattern is a higher energy, comminuted pattern. At time 0, the fracture line included the anterior cortical defect (A), but not the posterior cortical defect (B). At 1 week, the fracture line included the anterior cortical defect (C) but not the posterior defect (D). At 13 weeks, all bones demonstrated a highly comminuted pattern (E).

<table>
<thead>
<tr>
<th>RESORBABLE FILLERS</th>
<th>A</th>
<th>B</th>
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<tr>
<td><strong>T=0</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td><strong>1 Week</strong></td>
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<tr>
<td><strong>3 Months</strong></td>
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The resorbable fillers used in this study were 82% L-lactic acid and 18% PGA (polyactic acid/PGA) (Biomet, Inc., Warsaw, IN), a ratio that modulates the degradation rate for a predictable resorption and bone ingrowth process. Our histology demonstrates a controlled degradation of the resorbable screw, with simultaneous peripheral new bone formation, with no evidence of inflammation, sterile abscess formation, or bone lysis.

At present, the precise mechanism of the fillers’ protective effect is unclear. An interesting feature of the resorbable screws used in this study is that they swell slightly as they absorb water, which may prestress the hole and limit the local stress rising effect by changing the stress concentration around the hole. As metal fillers do not expand, this difference may explain the increased strength advantage of the resorbable screws at some data points over metal fillers. As cortical bone is weaker in tension than compression, the first failure occurs in tension where the forces are maximally oriented at a 45-degree angle to the long axis of the bone. Once a fracture initiates, it propagates along the 45-degree angle spiral path to the opposite cortex. In the resorbable-filled, but not the metal-filled, group, the fracture often missed the defect in one cortex. This may represent a strengthening effect, which redirects that fracture propagation away from the stress riser into intact bone. A second possible mechanism is that the presence of a screw mechanically links the anterior and posterior cortices, which would require that the whole bone fail as a single system, thereby raising the threshold for fracture. The fact that the metal screws do not resorb may increase their ability to link cortices at later time points, and may explain a higher percentage increase in load to failure in the metal group after 1 week. There is no evidence in our data that placing either a metal or resorbable screw increases the stiffness of the specimens.

There are obvious concerns with drawing clinical conclusions from an animal study. Rabbit bone physiology allows bones to heal more rapidly and fill holes more rapidly than human bones do. This fact, although detracting from our ability to draw direct clinical conclusions toward a human condition, means that the empty controls were filling in more rapidly than they would in the human condition. It is, therefore, more difficult to demonstrate a benefit when comparing these rapidly filling empty holes with the screw-filled holes. A second concern is that in our model, small bones were subjected to pure torsional loads; actual injuries occur in larger bones, at higher energy levels with complex loads. Despite this limitation, the carefully controlled nature of the mechanical testing allowed us to isolate the effect of the filled screw holes, revealing an intriguing protective effect of the filled versus empty holes, even at these low magnitude forces. Presumably, these mechanical features would apply to bones of any size. An additional limitation of the study is that although we demonstrate a protective effect of filling a single diaphyseal hole, clinical scenarios usually involve multiple holes, often at varying angles and screw sizes. Additionally, localized trauma from multiple screws or associated plates, disuse osteopenia, and local bone remodeling around an implant, all are clinical factors that contribute to actual refracture in patients. Follow-up studies and further work are necessary to evaluate the effect of filling multiple holes in larger bones.

The overall weakening effect of a removed screw in a clinical setting is a sum of the effect of the residual hole, which acts as a stress riser, and the microtrauma at the screw-bone interface caused by the removal process. Because the study design did not begin with removal of implanted hardware, we are unable to comment on the isolated destructive effect of screw removal. We are, however, able to show that the empty hole’s contribution to the weaker state of the bone after hardware removal is mitigated when that hole is filled with a resorbable screw.

In conclusion, any method of reducing stress risers and strengthening bone after hardware removal should satisfy two objectives. The first is to provide an immediate strengthening effect at the time of implantation compared with a hole left empty. The results of this study suggest that immediately after hardware removal, a bone weakened by an empty screw hole could be made stronger if the hole was filled with either a metal or resorbable screw. Filling the hole with a metal screw would defeat the purpose of hardware removal and would not satisfy the second objective, which is for the filler to allow for eventual replacement by bone. The resorbable fillers demonstrated no significant weakening effect during the resorption process, and our histologic analysis demonstrate early resorption and new bone formation without lysis.

If the two mechanisms for the strengthening effect of the filler are by (1) prestressing the hole and (2) linking the cortices, the ideal implant for reducing stress risers would swell slightly to prestress the holes, and maintain its ability to link both cortices of the screw hole as it is incorporated biologically. With further investigation, it may be possible to develop a protocol for mitigating the stress riser effect and raising the threshold for refracture after hardware removal.

REFERENCES

Early Experience and Results of Bone Graft Enriched With Autologous Platelet Gel for Recalcitrant Nonunions of Lower Extremity

Chao-Ching Chiang, MD, Chen-Yao Su, DDS, PhD, Ching-Kuei Huang, MD, Wei-Ming Chen, MD, Tain-Hsiung Chen, MD, and Yun-Hsuan Tzeng, MD

Background: Refractory nonunions of the tibia or femur are physically and mentally devastating conditions for the patients, and the treatment is challenging for orthopedic surgeons. The goal of this study was to assess the feasibility and outcome of surgical treatment in recalcitrant nonunions of a lower extremity with bone graft enriched with autologous platelet gel (APG).

Methods: Twelve patients with four femoral and eight tibial atrophic nonunions after multiple prior procedures were included. All of them were treated with the bone grafting procedures with autograft complex enriched with APG. They were evaluated with radiographs, bone mineral density for bony healing process, and the Short-Form 36 Health Survey for functional outcome.

Results: Of the 12 patients, 11 healed at an average of 19.7 weeks after the first attempt and 1 healed after the second attempt at 21 weeks. The bone mineral density increased from early healing to the remodeling phase. Of the 12 patients, 11 healed at an average follow-up of 32.4 months.

Conclusions: The results of this preliminary study implied the possible potential of bone graft enriched with APG in the treatment of recalcitrant nonunions of the lower extremity. More research is necessary to clarify its role in augmentation of bone graft to enhance healing of nonunion.

Key Words: Recalcitrant nonunion, Tibia, Femur, Autologous platelet gel.

platelets, which could be produced manually or automatically, in a small amount of plasma. The concentration of platelets in PRP is four to seven times above the baseline peripheral blood platelet levels. Cell adhesion molecules fibronectin, vitronectin, and fibrin are also contained within PRP. After mixing with the activator, such as thrombin and calcium chloride, PRP will generate APG and release the aforementioned growth factors. When APG is combined with the bone graft, it will support cell migration as a framework of osteoconduction throughout a bone graft in a bony defect. Besides, vascular ingrowth and epithelial migration will support the healing of a surgical wound. Several animal studies have shown the benefit and potential of APG for the treatment of skin burns, bone defects around dental implants, and oral and maxillofacial reconstruction. Some reports demonstrated clinical effect of PRP and APG in cosmetic surgery, cardiac surgery, and mostly in oral and maxillofacial surgery. Up to now, it has not been reported in the treatment of fractures or nonunions of the long bones. We present the feasibility and potential of APG to enhance bony union in recalcitrant atrophic nonunions of long bones.

**PATIENTS AND METHODS**

Between July 2002 and November 2003, 12 patients, 3 women and 9 men, at an average age of 50.5 (22–86) years, were treated with autologous bone graft complex enriched with APG (Table 1). This was a prospective study and the criteria for inclusion were atrophic nonunion of long bones in lower extremity, bone defect ≤ 2.5 cm, multiple prior procedures for treatment of fracture or nonunion, at least one failed prior autografting for aseptic nonunion or at least two failed autografting procedures for septic nonunion, and at least 6 months interval to last autografting. Preoperative evaluation included comprehensive review of treatment history, clinical assessment and biochemical testing (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) for possible septic nonunion, and radiographic diagnosis of atrophic nonunion. There were four femoral and eight tibial nonunions with an average fracture age of 24.6 (15–57) months. The patients had an average 4.3 (2–10) prior procedures, including 1.5 (1–2) failed prior autografting procedures. The average interval to last autografting was 7.6 (6–12) months. Seven of 12 patients were found to have initially open fractures (1 Gustilo type II, 3 type IIIa, and 3 type IIIb). Seven patients had complications with infection at presentation. Every patient was proved to have nonunion intraoperatively, and routine bacterial culture with biopsy was performed. Then, they were treated with the necessary procedures as indicated by their individual problems, including removal of previous implants, debridement, soft tissue reconstruction, fixation with internal or external fixators, and bone graft enriched with APG (Table 2). To treat aseptic nonunion, a one-stage operation was performed. For septic nonunion, staged operations were performed with at least 3 months interval to last debridement, and normal ESR and CRP values were confirmed before bone grafting. At the index bone grafting procedure, the size and extent of bony defect was estimated after debridement and fixation. For smaller defect (6 patients), cancellous autograft was harvested from the anterior or posterior iliac crest, depending on the availability after prior procedures. For larger defect (6 patients), graft complex consisted of cancellous autograft with allograft (3 patients) or Osteoset (3 patients; calcium sulfate by Wright Medical Technology, Arlington, TN). The autograft or graft complex was ready for mixture with APG.

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<th>Bone</th>
<th>Location</th>
<th>Open Fracture*</th>
<th>Fracture Age (mo)</th>
<th>Prior Procedures</th>
<th>Prior Autograft Attempts</th>
<th>Time to Last Autograft (mo)</th>
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<td>Smoker</td>
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</table>

* Gustilo classification.

DM, diabetes mellitus, DHS, dynamic hip screw.
Technique of Preparation of APG and Graft Complex

For each single processing, approximately 45 mL to 55 mL of the patient’s intravenous blood was withdrawn into a 60-mL syringe prefilled with citrate-based anticoagulant (5–7 mL ACD-A, Cytosol Laboratories, Inc., Braintree, MA). The blood was drawn before the commencement of surgery to prevent the activation of the coagulation system by surgery itself. Then, the blood was transferred to the blood chamber of the processing disposable and loaded into the centrifuge rotor cup of the SmartPReP Platelet Concentration System (Harvest Autologous Hemobiologics, Norwell, MA). A second processing disposable might be needed as indicated by the size of bony defect and was centrifuged simultaneously in the opposing rotor cup. By using an automated dual spin centrifuge, the blood was initially centrifuged at 3,650 rpm to separate the red blood cells from the blood plasma. When the centrifugation was decelerated to 60 rpm, the plasma decants automatically into the plasma chamber. Then, the centrifugation was accelerated to 3,000 rpm to form a layer of platelet concentrate in the bottom of the plasma chamber. The complete process took about 12 minutes to separate the anticoagulated whole blood into two chambers. The blood chamber contained the red blood cells. Thesecond plasma chamber contained platelet-poor plasma (PPP; supernatant) and platelet concentrate (a button-like precipitate). The upper two-thirds of the PPP was removed and could be used as hemostatic application. The platelet concentrate was then suspended in the residual PPP and concentrated PRP was created (Fig. 1).

Osteoset—bone substitute, pellets made of medical-grade calcium sulfate, by Wright Medical Technology, Arlington, TN. IF, internal fixator; EF, external fixator; AIC, anterior iliac crest; PIC, posterior iliac crest.

Table 2 Characteristics of Treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Surgical Method</th>
<th>PRP</th>
<th>Origin of Thrombin</th>
<th>Graft Complex</th>
<th>Origin of Autograft</th>
<th>Union Time (wk)</th>
<th>Follow-up (mo)</th>
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<td>Double</td>
<td>Bovine</td>
<td>Autograft + Osteoset</td>
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<td>21 (second attempt)</td>
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<td>Autograft + allograft</td>
<td>PIC</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>10</td>
<td>Debridement; EF+ bone grafting</td>
<td>Single</td>
<td>Autologous</td>
<td>Autograft</td>
<td>AIC</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>11</td>
<td>IF+ bone grafting</td>
<td>Double</td>
<td>Autologous</td>
<td>Autograft + Osteoset</td>
<td>PIC</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>12</td>
<td>Debridement; EF+ bone grafting</td>
<td>Single</td>
<td>Autologous</td>
<td>Autograft</td>
<td>PIC</td>
<td>19</td>
<td>24</td>
</tr>
</tbody>
</table>

Fig. 1. Preparation of APG. (A) Left blood chamber contained red blood cells and right plasma chamber contained upper PPP and lower PRP. (B) After removal of upper PPP, the platelet concentrate (a button-like precipitate) was suspended and concentrated PRP was created.

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to a dual cannula applicator. APG was generated through the mixture of the PRP and the activator. APG was then sprayed onto the autologous/allogous/synthetic bone graft to form the APG/graft complex. The complex was semisolid and sticky. Then, it could be cut to any shape to fit the individual bony defect, and was pasted as a whole layer between two sides of nonunion to form a bridge. For each individual procedure, after removal of previous implants, debridement, and application of new fixation device, residual APG was sprayed onto the rough surface of both ends of the bony defect and onto the soft tissue bed. Then, the precut APG/graft complex was applied and pasted. Another dual cannula containing the PPP and activator was sprayed into the soft tissue and incision wound. The drain was not routinely used. But in cases of soft tissue oozing and previous septic nonunion, the drain was placed at the margin of grafting materials and removed before 48 hours.

Postoperatively, all patients were followed up monthly for anteroposterior and lateral radiographs. Bone mineral density (BMD) was evaluated at the same level of both nonunion and contralateral bone at 3 days after operation as the baseline reference, and then at 1, 2, 3, 6, and 12 months. The position of the nonunion and contralateral limb were standardized by using an ankle-foot support frame to keep the patella facing up, which was approximately 15 degrees of internal rotation of legs. Images for BMD assessment were obtained with the Hologic QDR 4500-A bone densitometer (Hologic, Waltham, MA). The value of BMD (g/cm²) was calculated after manually drawing the nonunion level and the contiguous level with subtraction of the metal implant. The shape was similarly duplicated on the contralateral limbs (Fig. 2). The change of BMD at nonunion, contiguous level, and the same level of the contralateral limb was expressed as ratio to their baseline reference at 3 days after index bone grafting.

Functional outcome of all patients was assessed using the Short-Form 36 Health Survey (SF-36). At last follow-up, the patients were asked to complete the SF-36 questionnaire. Another recalled pretreatment SF-36 questionnaire was administered at the same visit.

Statistical analyses of BMD change at nonunion, contiguous, and contralateral levels and all eight preoperative and postoperative subscores of SF-36 were performed with the paired two-tailed Student t test. Significance was defined as \( p < 0.05 \).

**RESULTS**

After an average follow-up of 32.4 (24–40) months, 11 of 12 (91.7%) patients achieved radiographic evidence of solid union after the first attempt at a mean of 19.7 (17–22) weeks (Fig. 3). One patient (patient 4) with septic nonunion of femoral supracondyle was initially treated with staged operation of debridement, soft tissue reconstruction, external fixator, and APG bone grafting. Pin tract infection with local cellulitis developed at 8 weeks postoperatively. The external fixator was removed at 15 weeks, and the limb was protected with long leg splint. However, false motion developed after removal of the splint at 18 weeks. After antibiotic treatment, wound care, and fixation with Ilizarov external fixators, the second attempt of graft complex enriched with APG was performed. The patient achieved solid union at 21 weeks. No further operation or readmission was observed for the other patients after bone grafting, except removal of external fixators.

BMD change at nonunion level increased gradually throughout the 12 months and was higher than that in the contiguous and contralateral levels. They were 49.0%, 23.6%, and -5.5%, respectively, at 1 year (Table 3). Seven infected nonunions healed without recurrence of infection with regular clinical, ESR, and CRP assessments at each follow-up for at least 24 months. After bony union, patient 2 used a cane as walking assistance, and patient 4 walked with two crutches as a result of arthritic change of knee joint with stiffness (range of motion: 15–30 degrees).
All SF-36 subscores had improved after healing of non-union at last follow-up (Table 4). The changes in physical functioning, role physical, bodily pain, vitality, social functioning, and mental health were statistically significant after treatment. General health and role emotional did not change significantly.

**DISCUSSION**

More than 90% of patients with nonunions of long bone fractures can be treated successfully with one operative procedure. The patients with infected nonunions may require more than one procedure to eradicate the infection and heal the nonunion. For the treatment of nonunion of long bones, autologous platelet gel with autografting can be used. The outcomes of this treatment are promising, as demonstrated in the study by our team.

### Table 3 BMD Change at Different Sites

<table>
<thead>
<tr>
<th></th>
<th>1 mo</th>
<th>2 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonunion (%)</td>
<td>12.0 ± 6.4</td>
<td>21.4 ± 4.6</td>
<td>29.8 ± 15.3</td>
<td>39.9 ± 20.42</td>
<td>49.0 ± 31.9</td>
</tr>
<tr>
<td>Contiguous (%)</td>
<td>7.2 ± 11.1</td>
<td>8.9 ± 5.7</td>
<td>17.1 ± 13.2</td>
<td>19.2 ± 17.5</td>
<td>23.6 ± 20.0</td>
</tr>
<tr>
<td>Contralateral (%)</td>
<td>−1.1 ± 2.7</td>
<td>−3.7 ± 9.4</td>
<td>−8.50 ± 13.9</td>
<td>−5.2 ± 11.3</td>
<td>−5.5 ± 10.4</td>
</tr>
<tr>
<td>Nonunion vs. contiguous*</td>
<td>p = 0.213</td>
<td>p &lt; 0.001</td>
<td>p = 0.041</td>
<td>p = 0.014</td>
<td>p = 0.029</td>
</tr>
<tr>
<td>Nonunion vs. contralateral*</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation.
* Paired Student *t* test.

All SF-36 subscores had improved after healing of non-union at last follow-up (Table 4). The changes in physical functioning, role physical, bodily pain, vitality, social functioning, and mental health were statistically significant after treatment. General health and role emotional did not change significantly.

### Table 4 SF-36 Functional Outcome Before and After Treatment

<table>
<thead>
<tr>
<th>SF-36 Subscale</th>
<th>Physical Functioning</th>
<th>Role Physical</th>
<th>Bodily Pain</th>
<th>General Health</th>
<th>Vitality</th>
<th>Social Functioning</th>
<th>Role Emotional</th>
<th>Mental Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>15.8 ± 12.9</td>
<td>8.3 ± 12.3</td>
<td>25.7 ± 13.2</td>
<td>56.5 ± 21.0</td>
<td>49.6 ± 18.4</td>
<td>22.9 ± 13.9</td>
<td>13.9 ± 17.2</td>
<td>55.0 ± 15.8</td>
</tr>
<tr>
<td>After treatment</td>
<td>55.4 ± 30.5</td>
<td>41.7 ± 22.2</td>
<td>50.4 ± 19.6</td>
<td>59.4 ± 22.4</td>
<td>57.9 ± 17.8</td>
<td>60.4 ± 24.9</td>
<td>33.3 ± 31.8</td>
<td>61.3 ± 15.4</td>
</tr>
<tr>
<td>p*</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.206</td>
<td>0.023</td>
<td>&lt;0.001</td>
<td>0.067</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation.
* Paired Student *t* test.
bone, the option is individualized and must be addressed all factors of the problems of individual patients.25 Biologic factors include cell proliferation and differentiation to vascular regeneration. Biochemical factors include a cascade of cytokines and growth factors that appear, disappear, or get modified at the proper time of healing. Mechanical factors are crucial to provide the stability of bone fragment with appropriate mechanical condition to heal.23 Multiple techniques and materials (bone graft and bone graft substitutes) are currently used to treat nonunions.26 The techniques that include both nonoperative and operative procedures are as follows: low-intensity pulsed ultrasound, high-energy extra-corporeal shock wave, electric stimulation, percutaneous injection of autogenous bone marrow, internal fixators, external fixators, distraction osteogenesis, bone graft or bone graft substitute, vascularized bone graft, and use of osteoinductive molecules such as TGF-β, bone morphogenic protein, and PDGF.23

For the recalcitrant nonunions of long bone with failed prior autografting, the treatment is more challenging. After infection or multiple surgical procedures, the bone end and the soft tissue developed compromised blood supply. For segmental defect greater than 4 cm, more complex procedures, like the segmental transport of distraction osteogenesis24 or free vascularized bone graft,27 would be the optimal choice of treatment. For segment defect smaller than 4 cm, the gap of the nonunion site could to be filled with copious bone graft in an appropriate soft tissue bed. With the harvested autologous bone graft, it is sometimes inadequate and incapable of providing sufficient osteoinductive molecules and growth factors to heal the refractory nonunion. Although adding some allograft or synthetic bone substitute could increase the graft volume, they possess little potential of osteogenesis and osteoinduction as autologous bone graft.28 Recently, PRP has been thought to be one of the practical applications of tissue engineering. During the natural autologous bone grafting procedure, platelets inherently move to the graft and incorporate from the blood clot. After activation by the clotting, α granules in the platelets migrate to the cell membrane and release multiple growth factors, including PDGF, TGF, vascular endothelial growth factor, and EGF. These released growth factors could bind to the surface of mesenchymal stem cells, osteoblasts, endothelial cells, and other cells to enhance mitosis, differentiation, migration, and cell product formation.29 This process requires a living, healthy, and undamaged platelet. Some automatic systems are designed to harvest autologous PRP from a patient in approximately 15 minutes with efficiency in recovery of healthy platelets from a sample of whole blood. In addition to the growth factors released from the autologous platelets, the APG could be sprayed onto the nonunion site and surrounding soft tissue to form a favorable environment for revascularization and regeneration in bone and soft tissue. Adding the APG also increased the volume of graft complex for bridging the bone defect. The mixture of the APG/graft complex could be molded to the desired shape to fit the bone defect and bridge the ends.

In this preliminary study, unions were achieved in 11 of 12 patients after the first attempt, at an average of 19.7 weeks postoperatively. Increased rate of BMD at the nonunion site continued steadily to 1 year and was almost twice as that at the contiguous level of the same bone. However, BMD at the same level of contralateral bone seemed to remain relatively constant. During the operation, most of the APG/graft complex was applied or impacted to the nonunion site, and residual complex to the contiguous site to form a bridge. The increase of BMD suggested the progressive healing of nonunion from the early stage of regeneration to later remodeling.

However, disadvantages of APG should be considered for the possible carcinogenesis and disease transmission from bovine thrombin. There have been reports on the overexpression of therapeutic use of growth factors (including PRP) in relation to carcinogenesis.30 We do not use it in simple nonunion or other situations concerning surgery for soft tissue and bone tumor. Instead, we confine its use for some recalcitrant atrophic nonunion after failure of prior traditional autografting. We did not observe tumor growth or recurrence of infection in these patients. However, the follow-up was short, and this issue should be considered with caution for long-term results.

Another issue is the use of bovine thrombin, which is used together with calcium chloride as a clot initiator to activate PRP and PPP. The first concern is its possible linkage with Creutzfeldt-Jakob disease. In fact, Creutzfeldt-Jakob disease remained a disease isolated to the central nervous system. It has not been reported to be transmitted via blood or blood products. Another concern is about postoperative bleeding.31,32 Before 1997, bovine thrombin product contained bovine factor Va as a result of containment. The bovine factor Va induced human antibody and led to postoperative bleeding. In the first two patients, we used the purified bovine thrombin, Thrombin-JMI (King Pharmaceuticals, Inc., Bristol, TN) which do not contain bovine factor Va. For the last 10 patients, we used autologous thrombin from the thrombin generation device. We think autologous thrombin can completely erase the possibilities of disease transmission and cross-reaction from antibody.

Some drawbacks still existed in our study: lack of randomized control group and relatively short-term follow-up of limited patients. Simple nonunion of long bone is an ideal choice for a paired comparison when comparing the same patient’s failure to heal with prior orthopedic interventions with the results after some index therapy.33 Our patients had recalcitrant nonunions after failed prior autografting and were treated with autograft complex enriched with APG. The success of this index grafting procedure might be the possibility of having a synergistic effect of APG on graft complex. However, it was not exactly a perfect self-controlled study. Except the index treatment with APG/graft complex, they also received the other necessary procedures as indicated by

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their own problems. Thus, this study could not completely attribute the successful healing of nonunion to the addition of APG and justify it as a standard treatment. In considering treatment of our patients with prior failure of autografting, repeating the standard autografting procedure still included the risk of another failure. The source of autograft was also decreasing after repeated harvests. Under these circumstances, more complicated and extensive procedures like distraction osteogenesis and vascularized bone grafting could be considered. As a simple, reproducible, and new procedure in addition to the traditional autografting, APG has some attractive benefits but has not been studied in orthopedic surgery. Based on the support of basic research and successful clinical application of APG in other surgical fields, more research is required to further explore its potential and validate its effect in the treatment of refractory nonunion.

REFERENCES

Androstenetriol Immunomodulation Improves Survival in a Severe Trauma Hemorrhage Shock Model

Andreea C. Marcu, MD, Kristin E. Paccione, MS, R. Wayne Barbee, PhD, Robert F. Diegelmann, PhD, Rao R. Ivatury, MD, Kevin R. Ward, MD, and Roger M. Loria, PhD

Background: Traumatic shock activates the hypothalamic-pituitary-adrenal axis (HPA) to mediate a cascade of defensive mechanisms that often include overwhelming inflammatory response and immunosuppression, which may lead to multiple organ failure. Androstenetriol (5-androstene, 3β, 7β, 17β-triol-AET) is a metabolite of dehydroepiandrosterone that markedly up regulates host immune response, prevents immune suppression, modulates inflammation and improves survival after lethal infections by pathogens and lethal radiation.

Hypothesis: AET-induced immune modulation will improve survival in a conscious rodent model of traumatic shock.

Methods: A relevant traumatic shock rodent model that applies to both combat and civilian sectors was used. After creation of a midline laparotomy (soft tissue trauma), animals were hemorrhaged to a mean arterial pressure of 35–40 mm Hg. Resuscitation was initiated sixty minutes later with crystalloid fluid and packed red blood cells and animals were observed for two days. In a randomized and blinded fashion, AET or vehicle was administered subcutaneously at the beginning of resuscitation.

Results: In the vehicle group 5 out of 16 animals survived, (31%). In contrast, 9 out of 13 animals who received AET survived (69%), (Fisher Exact Test p < 0.05).

Conclusion: The results indicate that AET provides a significant protective effect and improves survival in a clinically relevant model of traumatic hemorrhagic shock. AET protective effects are associated with an elevation of Th1 and reduction of Th2 cytokines.

Key Words: Androstenetriol, trauma-hemorrhage, shock, survival, cytokines, immunomodulation.

The period immediately after acute injury is characterized by upregulation of proinflammatory cytokine expression leading to a later period of generalized immunosuppression. Among the neuroendocrine mechanisms involved in restoring homeostasis, the sympathetic nervous system plays a role in mediating acute counter-regulatory stress responses to injury. Using hemorrhagic shock as a model of acute stress, the sympathetic nervous system has been clearly identified for its role as a key component of the neuroendocrine response to stress.

This laboratory has previously reported that several native steroid hormones possess the ability to regulate the immune response, and thus, may offer a potential therapy against conditions associated with immune suppression and dysregulation resulting from trauma, hemorrhage, and sepsis. In vivo dehydroepiandrosterone (5-androstene-3β-ol-17-one, DHEA) and its downstream more potent metabolites, androstenediol (5-androstene-3β,17β-diol, AED) and androstenetriol (5-androstene-3β,7β,17β-triol, AET), decrease markedly the morbidity and mortality associated with infections from several diverse pathogens.

AET is the first known hormone that exerts an anti-inflammatory effect but also upregulates host resistance and counteracts the immunosuppressive effects of hydrocortisone.

Previous findings from this laboratory showed that AET provided significant survival effect in a 40%-volume hemorrhage trauma model. In view of this, experiments were undertaken to determine the effectiveness of AET in a more severe model of traumatic shock.
Although the primary purpose of this study was to determine whether administration of AET improved survival, we also attempted to gain insight into changes that might occur in the cytokine profile of animals as an initial means to understand the immunomodulatory effects of AET. For this reason, sequential measurements of levels of the pro- and anti-inflammatory cytokines, interleukin (IL) 2, 4, 6, 10, and 18 and interferon (IFN)-γ, in AET-treated and untreated animals were made.

**MATERIALS AND METHODS**

Adult male (300–375 g) Sprague-Dawley rats (Harlan Laboratories, Indianapolis, IN) were used in this study. All experiments were performed in adherence with the National Institutes of Health guidelines for the use of experimental animals and were approved by the Institutional Animal Care and Use Committee of Virginia Commonwealth University.

We used a nonheparinized model of trauma hemorrhage and resuscitation in the rat. Animals were anesthetized using isoflurane (Aerane, 3%–5% induction, 1%–3% maintenance, balance oxygen, USP, Baxter Pharmaceutical Products, Deerfield, IL) inhalation before the induction of trauma. Under sterile conditions, three catheters were placed in the carotid artery, jugular vein, and femoral artery (polyethylene PE 50 and PE 90 tubing, Portex, Hythe, Kent, England) followed by a 5-cm ventral midline laparotomy to induce soft-tissue trauma before the onset of hemorrhage. This soft-tissue injury has been shown to produce significant and early immune depression. The catheters were routed through to the nape of the neck and safely placed in a rubber cap, which was secured to the skin to prevent animals from manipulating the catheters after resuscitation and recovery. A morphine minipump (Alzet, Durect, Cupertino, CA) was inserted subcutaneously to provide clinically relevant amounts of analgesia during the entire experiment (approximately 0.1 mL of 50 mg/mL morphine with a delivery rate of 1 μL/h). The abdomen was closed in two layers using 3-0 silk suture (Sofsilk, coated, braided silk, Tyco Healthcare Group LP, Norwalk, CT). Between the muscle and skin layer, lidocaine hydrochloride jelly USP 2% (Akorn, Buffalo Grove, IL) was used to alleviate the pain throughout the experiment. Triple antibiotic ointment (Clay-Park Labs, Bronx, NY) was used to cover all incisions. Rats were allowed to awaken for at least 30 minutes after removal of anesthesia and achieving sternal recumbency. Hemorrhage was produced by removing blood from the carotid artery until the animal developed and sustained a mean arterial pressure (MAP) of 35 mm Hg to 40 mm Hg. This resulted in 83% of the animals having a blood loss of 45% to 60% of the total blood volume, with a minimum of 42% and a maximum of 64%. Hemorrhage to the target MAP took about 15 minutes, and then, the pressure was held between 35 mm Hg and 40 mm Hg for an additional 45 minutes with additional withdrawal of blood or infusion of saline. Any animal requiring a volume of saline to support pressure greater than the shed blood volume was considered to be in a state of cardiovascular collapse and immediately killed (Euthasol [pentobarbital sodium 390 mg/mL and phenytoin 50 mg/mL]; Virbac AH, Fort Worth, TX) and excluded from the study. Sixty minutes after the onset of hemorrhage, resuscitation was initiated with 0.9% sodium chloride (Baxter) in an amount equal to three times the shed blood volume. Morphine sulfate injection, USP 50 mg/mL (Abbott Laboratories, North Chicago, IL), was administered for pain treatment as an initial dose of 0.3 mg/kg. Immediately before starting the resuscitation, animals were randomized to receive subcutaneously either active drug (AET 40 mg/kg) or vehicle-methylcellulose (Hollis Eden Pharmaceutical, San Diego, CA). The chosen dose of AET was determined by previous studies that had shown that a single subcutaneous injection with 20 mg/kg of AET was protective in SWR/J mice infected with a lethal dose of 5 × 10^7 PFU of human coxsackie virus B4. Subsequent studies showed the 30 mg/kg AET was effective in protecting male mice from exposure to 8 Gy whole body radiation (a dose having 100% probability of causing death [LD50]). Because of the differences in the body weight and metabolic rates between mice and rats (±25 g vs. ±350 g, respectively), the dose of AET in this experiment was increased to 40 mg/kg. Computer-generated randomization was used to determine whether animals received drug or vehicle. To further eliminate bias, the study was blinded so that the investigators did not know to which group the rat had been assigned, until the conclusion of the study.

At 1 hour after the start of resuscitation, one-third of the shed blood volume was returned in the form of packed red blood cells (PRBC). MAP and heart rate were then observed for 3 hours, and blood samples were taken and analyzed for blood gases and lactate levels (ABL725 Series Analyzers; Radiometer, Copenhagen, Denmark) every hour after the resuscitation. These values were also determined before hemorrhage, posthemorrhage, and preresuscitation.

Blood samples were collected for cytokine analysis after trauma but before hemorrhage (prehemorrhage sample) and at 6 hours, 24 hours, and 48 hours postresuscitation. Animals were then monitored at 24 hours and 48 hours for MAP, heart rate, and blood gases.

Only animals that survived to 6 hours were included for study analysis. The rationale for this strategy was that the drug would require sufficient time to exert its immunomodulatory effect and that these effects would result in differences in delayed mortality. At the 48-hour time point, surviving animals were killed using Euthasol, and spleen tissue samples were collected for analysis of IL-2, IL-4, and IFN-γ.

**Rate Cytokine/Chemokine Measurements**

The LINCOplex kit (RCYTO-80K, Linco Research, St. Charles, MO) was used for the detection and measurement of cytokines IL-6 and IL-18. The overnight assay requires at least 5 μL of rat plasma. The standard curve ranges between 6.4 pg/mL and 20,000 pg/mL. The sensitivity for plasma is 1...
pg/mL to 20 pg/mL and the accuracy is between 92.8% and 108.6%. The Bio-Plex Manager Software (Bio-Rad, Hercules, CA) used employs StatLIA 4PL and 5PL curve fitting and provides percentage recovery calculations. Data produced by the software were analyzed and imported into SPSS (SPSS, Chicago, IL) for statistical analysis. Triplicate biologic samples were used to quantify the cytokine amounts. The IL-10 levels were detected using Endogen Rat IL-10 Elisa Kit (Pierce Biotechnology, Holmdel, NJ).

The tissue mRNA experiments were performed in the ABI Prism 7900 Sequence Detection System (Applied Biosystems, Foster City, CA) using the TaqMan (Applied Biosystems, Foster City, CA) One-Step PCR Master Mix Reagents Kit (P/N: 4309169). All the samples were tested in triplicates under the conditions recommended by the fabricant. The cycling conditions were 48°C for 30 minutes; 95°C for 10 minutes; and 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. The cycle threshold was determined to provide the optimal standard curve values (0.98–1.0). The probes and primers were designed using the Primer Express 2.0 version (Applied Biosystems). The probes were labeled at the 5’ end with FAM (6-carboxyfluoresceine) and at the 3’ end with TAMRA (6-carboxytetramethylrhodamine). Ribosomal RNA (18S rRNA) from the predeveloped TaqMan Assay Reagents (P/N: 4310893E) was used as endogenous control. Specific gene expression analysis was conducted using TaqMan probes to several gene products of interest (IFN-γ, IL-2, and IL-4).

**Statistical Analysis**

For survival data analysis, Fisher’s exact test and Kaplan-Meier test were used to determine significance. Cytokine data were analyzed using independent sample t test. All data are reported as means ± standard deviations.

**RESULTS**

**Physiologic and Metabolic Parameters**

As stated in Material and Methods, only animals that survived to 6 hours were included for study analysis. There were no significant differences in the number of animals not surviving to 6 hours between groups (2 AET and 1 vehicle-treated). The findings below represent data from animals surviving to 6 hours.

Baseline MAP was 120.7 mm Hg ± 6.7 mm Hg and 120.1 mm Hg ± 8.3 mm Hg in the AET and vehicle-treated animals, respectively, and demonstrated no significant difference.

After fluid resuscitation, an increase in MAP to a mean value of 79.7 mm Hg ± 5.7 mm Hg and 78.2 mm Hg ± 7.3 mm Hg was noted in the AET and vehicle-treated groups, respectively. At no time was MAP lower than 35 mm Hg to 40 mm Hg. After PRBC resuscitation, MAP improved to an average of 90 mm Hg. Of animals surviving to 6 hours, no significant differences between the two groups in MAP were recorded before returning animals back to the vivarium.

No significant differences in lactate levels at any time point were noted between groups. The mean lactate level at the end of hemorrhage was 15.6 mmol/L ± 2.92 mmol/L.

No significant differences were noted between groups for other blood gas parameters, including pH, PO2, PCO2, HCO3-, or base deficit.

**Effect of Androstenetriol on Survival**

The study contained a total of 29 animals that were randomized to receive either AET or vehicle. Of the 13 animals receiving AET, 9 survived, producing a survival rate of 69%, compared with 16 animals that received vehicle of which only 5 animals survived, producing a survival rate of 31%. The data were analyzed using both Kaplan-Meier survival analysis and Fisher’s exact test with both demonstrating significance, p < 0.05 (Fig. 1). Figure 2 shows the differences in survival at 6 hours, 24 hours, and 48 hours for both groups.

**Plasma Cytokine Measurements**

The available plasma samples collected were used for analysis of IL-6, IL-10, and IL-18, whereas the other cytokine
measurements (IL-2, IL-4, and IFN-γ) were processed from the spleen tissue samples collected at 48 hours.

No significant difference in IL-6 levels was noted between the groups at any of the time points. However, among the 13 survivors at 24 hours with levels of IL-6 below 400 pg/mL, 9 were treated with AET. Analysis of plasma IL-6 levels at 6 hours after the initiation of resuscitation showed that most animals with IL-6 levels below 400 pg/mL survived, whereas most animals with IL-6 levels above 400 pg/mL died, \( p < 0.025 \) (Fig. 3).

The effects of traumatic shock and AET on IL-10 levels are illustrated in Figure 4. Hemorrhagic shock markedly increased the levels of IL-10 in vehicle-treated animals; 1,262.2 pg/mL at 6 hours postresuscitation as compared with 479.9 pg/mL at 6 hours prehemorrhage, \( p < 0.001 \). However, at 6 hours postresuscitation, in the AET-treated group, IL-10 levels were significantly lower 280.5 pg/mL as compared with levels in the vehicle-treated group, \( p < 0.001 \). In addition, AET treatment reduced the levels of IL-10 from 479.9 pg/mL at the prehemorrhage time point to 280.5 pg/mL at 6 hours postresuscitation, \( p < 0.026 \). These results illustrate that AET treatment was associated with reduced IL-10 levels and prevented the marked increase mediated by hemorrhage.

The IL-18 measurements show considerable variability, and consequently, the differences observed between treatment groups are not statistically significant. However, maintaining low levels of IL-18 was consistent with sur-

\[ \text{IL-6 Levels above 400 pg/ml} \quad \text{IL-6 Levels below 400 pg/ml} \]

\[ \text{Fig. 3. (A) IL-6 threshold levels at 6-hour time point after trauma hemorrhage predicted the outcome of animals: survivors (S) and nonsurvivors (NS) at 24-hour time point,} \quad p \leq 0.025. \text{ The counts represent the levels of IL-6 at the 6-hour point. (B). Scatter representation of IL-6 values.} \]

\[ \text{Fig. 4. Reduction of interleukin 10 (IL-10) by androstenetriol. The drug was administered at the time of resuscitation. \#AET 6 hours postresuscitation/prehemorrhage,} \quad p < 0.026. \text{ *VEH 6 hours postresuscitation/prehemorrhage,} \quad p < 0.002. \text{ &AET/VEH at 6 hours postresuscitation,} \quad p < 0.001; \text{ independent sample test.} \]
vival after traumatic shock. This is illustrated by the results that show that at 6 hours, in the AET group, the mean level of IL-18 in survivors was 69 pg/mL ± 29.6 pg/mL as compared with 289.9 pg/mL ± 67.7 pg/mL in the AET-treated nonsurvivors. Similarly, at the same time point in the vehicle-treated group, surviving animals showed a mean IL-18 level of 49.6 pg/mL ± 17.4 pg/mL, whereas in nonsurviving animals the mean level was 224.1 pg/mL ± 275.9 pg/mL.

**Tissue Cytokine Levels**

Based on the levels of mRNA quantified in the spleen of AET- and vehicle-treated animals, results show that there is a significant increase in IL-2 mRNA levels ($p < 0.04$), with values of $29.5 \pm 9.0$ in the AET group and $17.7 \pm 1.3$ in the vehicle-treated group (Fig. 5).

A similar trend was evident for IFN-$\gamma$ with levels of $37.3 \pm 20.1$ in AET-treated animals as compared with $3.6 \pm 0.5$ in the vehicle-treated group. Because of the large SD in IFN-$\gamma$ measurements, these values are not statistically significant (Fig. 6).

The IL-4 mRNA measurement showed a decreased level in the AET-treated group ($22.3 \pm 7.1$) versus in the vehicle-treated animals ($38.4 \pm 8.3$, $p < 0.03$; Fig. 7).

**DISCUSSION**

As described in our previous study, we used a clinically relevant model of traumatic shock appropriate for both combat casualties and civilian trauma. These conditions include attributes of tissue injury and hemorrhage, avoidance of prolonged general anesthesia during the hemorrhage or resuscitation, and provision of clinically relevant analgesia. The model also provides for administration of clinically relevant amounts of crystalloid and PRBC as opposed to only crystalloid or whole blood or both. Although more challenging, the avoidance of general anesthesia in models of traumatic shock and resuscitation may be of particular importance when attempting to transition preclinical work to clinical studies. This is, in large part, because of the potential of anesthesia to affect the cellular metabolic, autonomic, cardiovascular, and microvascular response to pain, tissue injury, hemorrhage, and treatment. These alterations will, in turn, likely have an impact on the degree of downstream immune and inflammatory response, which may be linked to outcome. Thus, when examining immunomodulation as a treatment strategy for critical illness and injury, use of models that replicate the clinical setting with a high degree of fidelity is likely to yield results that are more definitive.

The results indicate that AET provides a significant protective effect and improves survival when administered subcutaneously as a single dose in a severe model of traumatic shock. In our previous experience in mice exposed to lethal infections, we have found that the effects of AED and AET are diminished when given orally, intravenously, or intraperitoneally as opposed to subcutaneously. This has led us to think that AET begins to exert its major effects through the cutaneous-embedded immune system also known as the skin-associated lymphatic tissues. These agents are effective when administered to epithelial surfaces, but are markedly less effective when administered into the circulation or by...
other routes. It is presumed that in the circulation androstenes are sulfated or bound to lipoproteins and rapidly cleared out. Administration by the subcutaneous route may cause the depot effect, thus increasing its activity time. Study is underway to improve delivery systems that would allow its intravenous administration. Finally, it is relevant to mention that pioneering studies reported that subcutaneous injection of radioactive hydrocortisone to rats or guinea pigs resulted in almost half of the administered dose being excreted in bile as conjugated metabolites within 1 to 2 hours.

Hemorrhage to target MAP of 35 mm Hg to 40 mm Hg amounted to a blood loss of 42% to 64% of the total blood volume and resulted in severe oxygen debts as evidenced by development of high lactate levels. Despite having identical oxygen debts at the end of hemorrhage and on return to the vivarium (as estimated by lactate levels), not all animals died or survived in each group. It is therefore likely that animals died of complications of reperfusion injury that are, of course, a complex milieu of events and mechanisms related to levels of acquired oxygen debt. This milieu includes combinations of inflammatory and immune events that lead to cell, organ, and whole animal death. Animals treated with AET after traumatic shock experienced greater than two-fold lower mortality compared with vehicle-treated animals. The mechanisms responsible for this improvement in survival are unclear but may be related to this neurosteroid hormone’s ability to modulate the immune and inflammatory response during the postresuscitation period.

The ability of AET to counteract (not inhibit) the immunosuppressive effects of corticosteroids may be particularly relevant to the setting of trauma where an imbalance in the level of these hormones may be a significant factor in the development of multiple organ failure. In addition, AED (androstenediol) and AET have the ability to suppress inflammation, just as other steroid hormones do, but without inducing immune suppression. Indeed, administration of DHEA to rodents after trauma hemorrhage restores the depressed cardiovascular and immunologic responses. Furthermore, AED has been reported to have significantly greater protective effects than DHEA has against lethal bacterial infections and endotoxin shock, as well as after trauma hemorrhage. In particular, AED has been shown to reduce the levels of corticosteroids in the circulation after influenza virus infection.

The exact mechanisms by which DHEA, AED, and AET exert a beneficial and a survival effect in the setting of trauma and hemorrhagic shock remain unclear. Strong evidence exists that the beneficial effects of DHEA (synthesized in the adrenal gland and secreted as the most abundant sex steroid in the body) is mediated via its interactions with estrogen receptors. Although DHEA is metabolized to AED and AET, the extent to which these two downstream metabolites function via estrogenic pathways similar to DHEA is unclear. Furthermore, many of the effects of AET and other traditional hormones are likely to be through cell-signaling mechanisms. This signaling can occur on very short time frames and is capable of widespread effects in very short time scales, a fact proven as well by our data showing effects as early as 6 hours postresuscitation. It is likely that these immunosteroids exert their effects via multiple pathways, including the peroxisome proliferators-activated receptor activators (PPARs).

One of the key functions of the PPARs in the immune system is the regulation of T-cell cytokine production. Reported observations of the PPARs in T cells showed that activation of PPARγ could inhibit the expression of IL-2 after T-cell activation and the production of IFN-γ. Therefore, by interfering with the differentiation of native T cells into their effector subsets, PPARγ could have a suppressive effect on the development of an immune response. Furthermore, it was shown recently that the presence of IL-4, a crucial cytokine for the development of Th2 cells, can induce the upregulation of expression of PPARγ in T cells, as well as cortisone. The cytokine profiles obtained in this study are suggestive of this mechanism.

Studies indicate that subcutaneous administration of the steroids DHEA, AED, and AET is associated with a rise in selective type 1 cytokines (IL-2, IL-3, and IFN-γ) as well as natural killer (NK) activity. Recently, it was reported that the induction of the IFN-sensitive response element sequences was strongly inhibited by dexamethasone, thereby the increase in IFN-γ mediated by AET could be one of the factors counteracting the immunosuppressive effect of glucocorticosteroids.

Immunomodulation during infectious disease processes and postoperative immunosuppression has been associated with shifts in the balance of cytokine profiles, resulting in the predominance of Th1 (IL-2, IFN-γ) or Th2 (IL-4, IL-10) cytokines. It has been shown that IL-2 and IL-4 have a fairly clear role on the immune response and are an indirect expression of the activity of the two T-helper subsets. Studies correlate the endogenous production of IL-4 with a poor prognosis in infected animals; moreover, the treatment with monoclonal anti-IL-4 antibodies markedly improved survival in sepsis experimental models. Indeed, in this study the results show that AET mediates a significant increase in IL-2 levels, a similar trend being evident for IFN-γ. IL-4 measurements showed a significant decreased level in the AET-treated group versus in vehicle-treated animals.

The cytokine IL-6 is produced by activated monocytes or T cells and has potent pleiotropic, immunomodulatory effects. The relevance of plasma IL-6 levels in traumatic shock and death has been reported by Mimasaka et al., and is an essential factor in postresuscitation recovery. Moreover, the influence of the neuroendocrine response on this cytokine after trauma was reported as well. Among the multiple different studies on the various cytokines, IL-6 has been shown to be the best reproducible predictor of mortality. Reports show that the circulating plasma levels
of IL-6 predict outcome in septic patients, with higher levels of IL-6 being associated with significantly increased mortality. As the mortality decreases, the IL-6 levels also decrease. As a result of the significant association between high circulating serum IL-6 levels, mortality, and multiple organ dysfunction syndrome, IL-6 is widely thought to be detrimental.38 However, the effects of IL-6 in conscious animals in the absence of infection or lipopolysaccharide challenge has not been studied in great detail. The results from our current study using a model of traumatic hemorrhage without sepsis show a threshold concentration of IL-6 as well. IL-6 levels below 400 pg/mL were associated with a significant increase in survival and IL-6 levels above 400 pg/mL with mortality (Fig. 3).

The controversy on the systemic role of IL-10 in trauma hemorrhage is not resolved at this time; its dual role has been recently reported by Schneider et al.39 IL-10 is an important immunoregulatory cytokine produced by B and T lymphocytes, monocytes, and macrophages. These cells rapidly secrete IL-10 in response to stress, suggesting an important counter-regulatory role for this anti-inflammatory cytokine.40 Previous studies reported a controversial role of IL-10 after traumatic injury, shock, or sepsis. Some studies suggest that IL-10 is an immunosuppressive mediator after injury or sepsis, being deleterious because of its ability to suppress cell-mediated immune responses, whereas others suggest that IL-10 is an important regulator of the proinflammatory response, having a beneficial effect on outcome postinjury.39 Our results are in accordance with these previous studies and show a marked elevation of plasma IL-10 levels in the early stage of trauma hemorrhage (6 hours after trauma hemorrhage) in the vehicle-treated animals, whereas AET treatment at the same time point reduced IL-10 levels below prehemorrhage values, demonstrating once again the rapid immunomodulatory effects of AET.

IL-18 (formerly IFN-γ-inducing factor) is a potent proinflammatory cytokine involved in the regulation of cell-mediated and innate immune responses to infection, trauma, and inflammation. IL-18 is able to induce IFN-γ, granulocyte-macrophage colony stimulating factor, tumor necrosis factor-α, and IL-1 in immunocompetent cells, activate killing by lymphocytes, and to upregulate the expression of certain chemokine receptors. The ability of IL-18 to enhance IFN-γ production by NK cells is dependent on the presence of IL-12.41 IL-18 has been also shown to strongly augment the production of IFN-γ by T cells and NK cells,42 with IFN-γ being an established survival factor in sepsis in both humans and mice.43 Our results suggest that maintaining low levels of IL-18 may be consistent with survival after trauma and hemorrhagic shock. One could speculate that the increase in IFN-γ levels in AET-treated animals may be associated with a feedback inhibition resulting in low IL-18 levels and survival.

It should be stressed again that the main purpose of the current study was to test the ability of AET to improve survival after severe traumatic shock. Because of the high mortality associated with the insult, it was not possible to obtain equal sample numbers at each time point between groups or often sufficient biologic samples at each time point when animals survived. The reasons for various differences in the group numbers for the cytokine analyses is because of differences in survival and ability to obtain cytokines counts to make both groups equal. The use of tissue mRNA for IFN-γ, IL-2, and IL-4 analysis was resorted to because in the rat we found the performance of LINCOplox analysis system to be highly variable and inconsistent. As a result, only one time period could be used for the tissue analysis of these cytokines.

Determining the Th1-Th2 balance throughout the postresuscitation period in this study in each group is thus problematic. Only further studies designed to examine all factors at each time point can provide more definitive data. The current study does support the concept that, regardless of group, survivors appear to respond to the insult by producing some cytokine profiles indicative of immune restoration. However, on the basis of the differences in survival between groups, it can be argued that AET may cause this to happen more often and perhaps turn nonresponders to responders.

**CONCLUSION**

AET treatment significantly improves survival after trauma and hemorrhage when administered subcutaneously. Simultaneously, AET appears to mediate a reduction in Th2 and an increase in Th1 cytokines, as evident by the lower levels of IL-4, IL-6, IL-10, and IL-18 and an elevation of IFN-γ and IL-2 levels. These results show that immune modulation may be a significant factor in survival after trauma hemorrhage and shock.

**ACKNOWLEDGMENTS**

We thank Dr. Matthew J. Beckman for his assistance and guidance in performing the mRNA analysis. Also, thanks to Marcus Skaflen for his technical support.

**REFERENCES**


Two Cohorts of Severely Injured Trauma Patients, Nearly Two Decades Apart: Unchanged Mortality But Improved Quality of Life Despite Higher Age

Johanna M. M. Nijboer, MD, Corry K. van der Sluis, MD, PhD, Joukje van der Naalt, MD, PhD, Maarten W. N. Nijsten, MD, PhD, and Hendrik-Jan ten Duis, MD, PhD

Background: The care for trauma patients has undergone major changes during the last decades. Among these changes are the institution of Advanced Trauma Life Support, transport of patients by helicopter, and damage control surgery. In the Netherlands, the designation of Level I trauma centers and mobile medical teams in 1999 have upgraded trauma care. Not only has medical care undergone changes, numerous injury prevention measures have also been established during the last 20 years. Primary prevention measures include speed limits, improved right of way rules, banned use of a mobile phone by drivers, enhancement of infrastructure, campaigns to promote road safety and dissuade the use of alcohol, and stricter police control. Among secondary prevention measures were the institution of legislation to require motorcycle and moped helmets, seatbelts, and baby chairs for bicycles and motor vehicles, and the increased safety of vehicles.1

Methods: Two cohorts of trauma patients with an Injury Severity Score >15, treated at the University Medical Center Groningen were compared. The first cohort was treated from 1985 to 1990, the second cohort from September 2002 to January 2005.

Results: The annual mean number of severely injured patients increased by 76%. Fourteen percent more patients had sustained an injury at home. The mean age increased from 33 ± 22 years to 41 ± 23 years. The presence of severe head and neck injuries in the patients increased from 62% to 73%. Inhospital mortality remained unchanged at 25%. The outcome of survivors improved; 67% of patients made a moderate or good recovery versus 40% almost 20 years ago.

Conclusions: Striking are the consequences of the aging of the Dutch population: an almost 10-year increase in mean age and a rise in severe head and neck injuries in the population treated at our trauma center. The unchanged mortality and improved outcome of survivors represented the enhanced trauma care.

Key Words: Trauma, Multiple injuries, Injuries, Mortality, Glasgow Outcome Scale.

The care for trauma patients has undergone major changes during the last decades. Among these changes are the institution of Advanced Trauma Life Support, transport of patients by helicopter, and damage control surgery. In the Netherlands, the designation of Level I trauma centers and mobile medical teams in 1999 have upgraded trauma care. Not only has medical care undergone changes, numerous injury prevention measures have also been established during the last 20 years. Primary prevention measures include speed limits, improved right of way rules, banned use of a mobile phone by drivers, enhancement of infrastructure, campaigns to promote road safety and dissuade the use of alcohol, and stricter police control. Among secondary prevention measures were the institution of legislation to require motorcycle and moped helmets, seatbelts, and baby chairs for bicycles and motor vehicles, and the increased safety of vehicles.1

Tertiary prevention measures included the institution of a national emergency phone number to reduce response times and the aforementioned upgraded trauma care. The objective of these medical and societal efforts was to prevent traumatic incidents and injuries, and in case of casualties to reduce mortality and morbidity. The nationwide reduction of traffic deaths from almost 11 per 100,000 inhabitants per year in the mid 1980s to less than 6 deaths per 100,000 inhabitants, despite a rise in mobility of almost 25 billion miles per year, in 2004 is clear.2 Until now, it has not been known if all aforementioned goals have been achieved. For example, international literature describes a range from unchanged to improved outcomes after trauma center implementation.3–6 However, we think that the Dutch trauma population, with its low proportion of penetrating injuries, differs from most published populations. The aim of our study was to assess in which way the sustained efforts have altered trauma mechanisms, occurrence of injuries, treatment, and outcome in two cohorts of severely injured trauma patients, almost two decades apart.

MATERIALS AND METHODS

Two cohorts of trauma patients treated at the University Medical Center Groningen, University of Groningen, a Level I trauma center, were analyzed. The first cohort was treated from January 1985 to January 1990 (60 months), the second cohort was treated from September 2002 to January 2005 (28 months). Data were extracted from the trauma center’s
trauma registry database, which contains all primary and secondary admitted trauma patients of all ages with an Injury Severity Score (ISS) >15 and positive signs of life on arrival to the trauma center. The inclusion of patients in the trauma registry and collection of data were performed by a small number of trauma attending physicians and based on strict guidelines. As a result, the quality of data was high, without a significant number of missing patients or data.

The collected patient data included gender, age, mechanism of injury, duration of prehospital phase and mode of transport, diagnosis, ISS, Maximum Abbreviated Injury Scale (MAIS), treatment, number of days on respirator, Intensive Care Unit (ICU) stay and total hospital stay, inhospital mortality, Glasgow Outcome Scale (GOS) score at discharge, and discharge destination.

The ISS was based on the 1998 Abbreviated Injury Scale (AIS) scores for each body region. An injury to a body region was considered severe in case of an assigned AIS score >2. The most severely injured body region was defined by the highest AIS score, the MAIS, and categorized as follows: head and neck, thorax, abdomen, extremities. In case a patient sustained multiple injuries with identical AIS scores, the MAIS body score was classified according to risk of death: head and neck > thorax > abdomen > extremities.9 The GOS quantifies functional outcome ranging from death (GOS score 1) to mild or no disability (GOS score 5).

Statistical Analysis

Data were expressed as mean ± SD or as median in the case of a skewed distribution. Differences between groups were assessed with the Student t test or the Mann-Whitney U test. Associations were assessed with the χ² test, Fisher’s exact test, or the binomial test. Differences were considered significant for a two-tailed p value < 0.05. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) version 12.0.1 for Windows.

RESULTS

Demographics

From 1985 to 1990 (the first cohort) 748 trauma patients with an ISS >15 were admitted to the hospital, an average of 150 patients per year (Table 1). From 2002 to 2005 (the second cohort), an average of 264 patients with an ISS >15 were admitted to the trauma center annually, leading to a total of 615 patients and a mean increase of 76%. The second cohort was significantly older than the first cohort with a mean age of 41 ± 23 years (median of 39 years) versus a mean age of 33 ± 22 years (median of 26 years). Figure 1 illustrates the changed distribution of age in the studied cohorts. The male to female ratios remained unchanged; approximately three quarters of the patients were male.

The trauma mechanisms have also changed (Table 1). In the second cohort, 57% of the patients sustained their injury in traffic, whereas in the first cohort, 76% of the patients were traffic casualties. The distribution of involved vehicles (car, truck, motorbike, moped, bicycle, pedestrian) did not change significantly. In the second cohort, more people were injured at home than were people in the first cohort: 23% versus 9%. The age in this subgroup of patients injured at home has dramatically increased from 33 ± 22 years to 52 ± 25 years. Similarly, those who were injured at work in the second cohort were also older; an increase in age from 25 ± 17 years to 45 ± 16 years.

Prehospital Data

In the first cohort a mean of 45 ± 41 minutes elapsed between the trauma incident and arrival of patients directly referred to the trauma center. All patients were transported by ambulance. The prehospital phase of directly referred patients of the second cohort lasted longer (p < 0.001): 82 ± 58 minutes, even though 12% of the patients was transported by helicopter. Additionally, fewer patients were secondarily referred from a local hospital: 28% of the second cohort versus 35% of the first cohort (p = 0.005). Approximately all patients of both cohorts were referred from the local hospital to the trauma center within 24 hours after sustaining the injury.

Injuries

Proportionally, a strong reduction of injuries to all AIS body regions was noticeable in the second cohort; except for head and neck and facial injuries, for which occurrences have remained similar. The second cohort was slightly less severely injured according to the ISS than the first cohort was: a mean of 25 ± 10 versus a mean of 28 ± 21 (p < 0.001). In the second cohort, fewer AIS body regions were severely affected per patient than in the first cohort: 1.5 ± 0.7 (median 1) versus 1.9 ± 0.9 (median 2) (p < 0.001). This reduction accounted for all trauma mechanisms. Nevertheless, in cases of head and neck injuries, a severe injury was more often included (Fig. 2). Seventy-three percent of the patients in the second cohort suffered from severe head and neck injuries, in

### Table 1 Demographic Data of Both Cohorts

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<thead>
<tr>
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<tr>
<td>No. patients</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>748</td>
<td>615</td>
<td></td>
</tr>
<tr>
<td>Mean/yr</td>
<td>150</td>
<td>264</td>
<td></td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>76%</td>
<td>72%</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)*</td>
<td>33 ± 22(26)</td>
<td>41 ± 23(39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of accident (% of patients)</td>
<td></td>
<td></td>
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<tr>
<td>Traffic</td>
<td>76%</td>
<td>57%</td>
<td>&lt;0.001</td>
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<tr>
<td>Home</td>
<td>9%</td>
<td>23%</td>
<td>&lt;0.001</td>
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<tr>
<td>Work</td>
<td>6%</td>
<td>7%</td>
<td>NS</td>
</tr>
<tr>
<td>Sport</td>
<td>3%</td>
<td>7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>5%</td>
<td>6%</td>
<td>NS</td>
</tr>
<tr>
<td>Unknown</td>
<td>1%</td>
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* Mean ± SD (median). NS, not significant; p > 0.05.
contrast to 62% of the patients in the first cohort ($p < 0.001$). In absolute numbers of patients (mean/year), this rise is even more striking: 94 patients in the first cohort versus 189 patients in the second cohort. The occurrences of severe chest, abdominal, and extremities injuries showed significant reductions in percentages but in absolute numbers per year the occurrence of severe injuries to these AIS body regions have remained static. The number of patients with severe facial injuries or injuries to the “external” region was too small to be statistically relevant.

**Clinical Course**

Regarding treatment, patients were less often operated on in the second cohort: 45% of the patients underwent one or more surgical procedures versus 59% of the patients in the first cohort ($p < 0.001$). Sixty-two percent of the second cohort was admitted to the ICU, which is almost 10% less than in the first cohort (Table 2). The length of the ICU stay has remained stable at 9 days. A smaller percentage of the ICU patients was intubated and mechanically ventilated in the second cohort when compared with those in the first cohort: 79% versus 93%; however, the duration of intubation has increased from 7 to 9 days.

**Mortality**

The mortality rate was equal in both cohorts: 24% to 25% (Fig. 3). This accounted for all subgroups of mechanisms of trauma. The causes of death have not significantly

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**Fig. 1.** Distribution of age (in years) of both cohorts.

**Fig. 2.** Distribution of total injuries and severe injuries per AIS body region in percentage of patients of both cohorts. AIS, Abbreviated Injury Score.
changed. Approximately 60% of deaths in both cohorts were caused by cerebral injury. Uncontrolled hemorrhage (approximately 12% in both cohorts) and respiratory failure (10% in both cohorts) were other leading causes of death. However, the time to death has increased ($p < 0.001$). The mean time between arrival to the trauma center and death of the second cohort was 4.2 ± 8.3 days, median 0.9 days, whereas it was 1.5 ± 8.4 days, median 0.2 days, in the first cohort. The age of the nonsurvivors increased from 38 ± 25 years in the first cohort to 47 ± 25 years in the second cohort ($p < 0.001$), but their ISS diminished from 42 ± 20 to 32 ± 12 ($p < 0.001$). Regarding mortality per MAIS, the only significant change occurred in the head and neck region: in the first cohort, 38% of these patients died, in contrast to 29% in the second cohort ($p < 0.001$). In other MAIS regions, the mortality remained stable at approximately 10% to 15%.

**Outcome of the Survivors**

In the second cohort the total hospital stay was shorter when compared with that of the first cohort: 24 ± 26 days versus 19 ± 21 days, respectively (Table 2). The outcome of survivors at discharge has significantly improved in the second cohort (Fig. 3). Although the percentage of patients in a vegetative state (GOS score 2) has remained stable at approximately 2%, the percentage of severely disabled patients (GOS score 3) has strongly diminished from 32% to 7% ($p < 0.001$). An increased percentage of patients, from 40% to 67%, made a good recovery (GOS scores of 4 and 5) ($p < 0.001$). This phenomenon accounted for all MAIS regions: a 20% to 30% rise in patients making a good recovery. For the MAIS head and neck region, this concerned an increase from 34% to 64% ($p < 0.001$). This was the result of a large reduction in severely disabled patients, from 24% in the first cohort to 6% in the second cohort. Furthermore, the incidence of GOS score 2 has remained stable at approximately 3%. Only slight shifts have occurred in discharge destination.

**DISCUSSION**

The data presented demonstrate that during the last 20 years many changes have occurred. Although road traffic incidents still are the leading cause of injury, more people sustained injuries at home. Besides the increased number of treated patients, the almost 10-year increase in the mean age of the second cohort is impressive. Also remarkable is the almost 10% increase in the incidence of severe head and neck injuries. In terms of morbidity, the outcome of survivors has dramatically improved because 67% made a moderate or good recovery. The proportion of nonsurvivors did not change during both study periods. Apparently, the improvements in trauma care during the last 20 years are not reflected by the quantity of lives saved but by the quality of lives saved.

**Increased Patient Load**

Striking is the 76% increase of severely injured patients admitted to the trauma center. Previous publications have described an increase in severely injured patients treated in a newly implemented trauma center.4,5 However, the designation as a trauma center did not expand the catchment area of

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**Table 2 Duration of Intubation, Length of Stay at the Intensive Care Unit, and Inhospital Stay**

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<tr>
<td><strong>Intubation</strong></td>
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<tr>
<td>Patients (%)</td>
<td>77</td>
<td>57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration*</td>
<td>7 ± 11 (3)</td>
<td>9 ± 13 (4)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Intensive care admission</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients (%)</td>
<td>71</td>
<td>62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay*</td>
<td>9 ± 13 (5)</td>
<td>9 ± 13 (4)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Total hospital stay</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay*</td>
<td>24 ± 26 (17)</td>
<td>19 ± 21 (12)</td>
<td>0.007</td>
</tr>
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</table>

* Days, mean ± SD (median).

NS, not significant; $p > 0.05$.  

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**Fig. 3. Distribution of Glasgow Outcome Scale scores in percentage of patients of both cohorts.**
the hospital. Furthermore, the number of inhabitants of the region has only increased by 7% from 1.6 million in the mid 1980s to 1.7 million in 2002. Most likely, the increased number of patients is the result of the strict guidelines for triage and secondary referrals implemented with the nationwide designation of 10 trauma centers. Before the designation, triage was performed at random by the attending paramedics. Our results show an increased percentage of primary referred patients as the result of the more effective prehospital triage. A consequence of the catchment area that constitutes almost one quarter of the countries’ area, is the rather long prehospital phase. Even though a significant number of patients were transported by helicopter, transport times are rather long. The prolonged prehospital phase is in agreement with the insights of delivery of high care to the trauma scene (“stay and play”) instead of the “scoop and run” tactics in previous decades. A similar trend was seen in the United Kingdom. The aforementioned improved prehospital care, combined with diminished response times after institution of a national emergency phone number may have reduced the number of people succumbing before reaching the hospital. Unfortunately, verification of this hypothesis is not possible because accurate data on prehospital deaths are not available.

### Shift in Trauma Mechanisms and Injuries

In accordance with the countries’ decreasing number of road traffic incidents, fewer severely injured traffic casualties were admitted to the trauma center. Preventive measures have reduced the number and severity of traffic incidents. However, a rising number of elderly people sustained severe injuries at home. Nationwide, almost three quarters of all trauma incidents happening at home involve people more than 70 years of age. In 75%, it concerns a fall that may or may not have been from height. Striking is the increased incidence of severe head and neck injuries to 73% of all patients. This phenomenon is not limited to the Netherlands, as Kannus et al. described similar results for Finland. Besides balance disturbances and less ability to anticipate to a fall, the preinjury widespread use of anticoagulants of elderly people may play an important role in causing intracranial bleedings.

Lower ISSs were encountered in the second cohort. To conclude that the cohort was less severely injured would be premature. Inherent to the ISS formula, the smaller number of affected AIS body regions reduced the ISS. Our impression is that the change in trauma mechanisms diminished the number of injured body regions, but increased the severity of the sustained injuries: in other words, a shift from patients with multiple injuries to patients with severe isolated injuries.

### Outcome

The unchanged mortality rate is disappointing at first sight. However, outcome after trauma is determined by time to definitive care, quality of care, injury severity, and host factors. The current cohort greatly differed on these points from the 1985 to 1989 cohort. The time to definitive care was prolonged, but the quality of care is expected to have greatly improved. A statement on injury severity is difficult because the ISS was roughly unchanged, with a reduction of the number of body regions affected and altered distribution of severe injuries. Most important is the aforementioned increase in severe head and neck injuries, which are known for their poor outcome. Host factors include gender, age, and preinjury medical state. Gender was unaffected, contrary to an increase in age of almost 10 years. This large increase in age is expected to have entailed extensive comorbidity. Analysis by Milzman et al. showed an increased mortality rate based on preexisting conditions that were independent of age and ISS. Additionally, it has been well documented that, even in the absence of comorbidity, the risk of adverse outcomes increases with age, independent of other variables.

With improved medical care on the one hand and the changed injury patterns plus worsened host factors on the other, the mortality rate was unaffected. However, the prolonged time to death may be indicative of enhanced prehospital and inhospital trauma care. With all improvements in care it appears that we were able to keep the patient alive during the most life-threatening phase, but unfortunately we did not save more lives in total.

We conclude that large advances have been made in trauma care, but the aging of patients and increased incidence of severe head and neck injuries has annulled the life-saving effect. Having dealt with major issues in the 20th century, in the current century a new hurdle in trauma care needs to be cleared: the management of an extending geriatric population that is severely injured after only a minor traumatic incident. Future preventive and protective measures should focus on elderly patients at home and altered care strategies should be considered.

Our study has several limitations, mostly because of its retrospection. Patients were identified from a trauma registry, fortunately without a significant amount of missing data. Unfortunately, only data concerning the trauma center have been analyzed, no data were available on casualties who were not treated in our facility. Another shortcoming is that some relevant items (e.g. complications and level of prehospital care) could not be analyzed because it was not scored in the first cohort. Analysis of outcome of survivors by means of the GOS is not preferable in patients without a traumatic brain injury. However, in this study, this concerned only a small minority of patients and other validated outcome scores (for example the sickness impact profile) have not been scored in the first cohort. For the same reason the successor of the GOS, the extended GOS, was not suitable either. A study to assess outcome in detail 1 year after the injury is in progress. Nonetheless, our data disclose valuable insights regarding severely injured trauma patients.

### CONCLUSION

During the last 20 years many changes have occurred. The rise in severe head and neck injuries, the unchanged mortality, and the almost 10-year increase in mean age, are
inextricably bound with one another. The outcome of survivors has dramatically improved because 27% more patients made a moderate or good recovery. The improvements in trauma care are not reflected by the quantity of lives saved but by the quality of lives saved.

REFERENCES

Availability of Trauma Specialists in Level I and II Trauma Centers: A National Survey

Young-Ju Kim, RN, ACNP, PhD, Yan Xiao, PhD, Colin F. Mackenzie, MB, ChB, FRCA, FCCM, and Sharyn D. Gardner, PhD

Background: Despite American College of Surgeons Committee on Trauma’s criteria, little data exists about the variability of practices in both the composition of trauma teams and timing of specialist availability across trauma centers. The purpose of the study was to determine the availability of trauma team personnel in Level I and II trauma centers across the United States.

Methods: Two surveys were developed and mailed to trauma directors and coordinators in 450 centers. Responses were received from 254 directors (56%) and 218 coordinators (48%). The director survey was designed to collect data on trauma team composition and timeliness in response to a hypothetical scenario. The coordinator survey was designed to collect data on trauma center characteristics and general availability of trauma specialists.

Results: Eighty-two percent of Level I and II centers had trauma surgeons available within 15 minutes of and 37% at patient admission. The in-house (IH) centers (60%) had a trauma surgeon at patient admission significantly more than on-call centers did (22%). The specialty surgeons, such as neurosurgeons (73%) and orthopedic surgeons (75%), were mostly available through the on-call system. An IH system, high volumes of trauma patients, and designation by American College of Surgeons were significantly associated with higher likelihood of trauma surgeons physically present at the bedside within 15 minutes.

Conclusions: There was a large variation in the availability of expertise at or shortly after a trauma admission. For centers with low patient volume, early triage, better notification systems based on advanced telecommunication technology, and compensation for IH call may be a solution to better use the trauma surgical specialties.

Key Words: Call system, Coordination, Trauma system, Trauma surgeon, Trauma specialist

availability of trauma specialists in trauma centers

Data Collection

Survey questions for trauma specialist availability were developed from a review of the literature as well as interviews conducted with trauma directors and staff of 13 trauma centers across the United States. These centers consisted of 11 Level I centers, 1 Level II trauma center, and 1 specialty clinic. Of these 13 centers, 1 was ACS-designated, and the rest were state-designated trauma centers. Five centers reported more than 2,000 admissions a year, five centers 1,001 to 2,000 admissions, and two centers less than 1,000 admissions. From these interviews and review of the literature two separate surveys were developed, one for trauma directors and one for trauma coordinators.

The trauma director survey was designed to collect information about trauma team composition and timeliness. A hypothetical trauma scenario was used to solicit information on the process of assembling specialists. The scenario described a pending admission of a patient with high-severity injury.

It’s Friday, 7 PM. A 36-year-old intoxicated man is trapped in the driver’s seat of a sports utility vehicle that fell 20 feet off a bridge. He is moaning, and has shallow and rapid breathing, with heart rate of 120 beats per minute and blood pressure 85/30 mm Hg. Both of the driver’s legs are trapped under the dashboard. The crash site is 10 minutes from your trauma center. Intravenous access has not been obtained.

The trauma directors were asked to check whether a trauma surgeon, emergency medicine physician, anesthesiologist, emergency medicine technician, respiratory therapist, radiology technician, and nurse were available upon patient arrival, within <5 minutes, <15 minutes, <30 minutes, or not applicable. The trauma directors were also requested to indicate whether the presence of specialists is regulated by the trauma center’s protocol or by judgment of needs.

The trauma coordinator survey was designed to gather data regarding each trauma center’s characteristics such as ownership (private or public, etc.), trauma center level, designation type, number of trauma patient admissions, number of resuscitation bays, number of trauma clinicians, and the general availability of trauma specialists. The category of specialists included trauma surgeons, anesthesiologists, emergency medicine physicians, radiology technicians, respiratory therapists, trauma nurses, and specialty surgeons. The general availability was indicated by five levels: not available to trauma services, OC availability more than 30 minutes, OC less than 30 minutes, IH covering trauma and nontrauma services, and IH dedicated to trauma services.

The survey questionnaires were mailed respectively to trauma directors and coordinators in the identified 450 Level I and Level II trauma centers in May 2003. A random four-digit number generated by a third party not involved in the research was assigned to each trauma center to ensure respondent centers’ anonymity. Self-addressed business reply envelopes were used for returning surveys directly to the research team. Five weeks after the first mailing, a second mailing was sent out to nonrespondents.

Analysis Approach

Availability of trauma specialists was analyzed by trauma center level (Level I vs. II), designation type (ACS vs. state), and four levels of admission volume: low (<500), medium (500–1,000), high (1,001–2,000), and extremely high (>2,000). The differences among groups were assessed by appropriate Student’s t tests and χ² tests.

RESULTS

Characteristics of Trauma Centers

Of the 450 identified trauma centers, we received responses from 308 (68.4%) centers. The response rate of trauma directors was 56.4% (254 of 450 centers), and 48.4% (218 of 450 centers) for trauma coordinators. The responses in this study represent all states with the exception of Idaho and Kentucky, both of which did not provide information regarding their trauma centers. Furthermore, although we did identify trauma centers for Alabama, Hawaii, Kansas, and Vermont, these four states did not return any of our mailed surveys (Table 1).

Trauma centers were mostly state-designated; 61% of Level I and 67% of Level II trauma centers (Table 2). Half of the trauma centers had more than 1,000 trauma admissions during the 2001 to 2002 fiscal year. Level I centers had more than 1,700 patients on average admitted annually, more than twice of that of Level II centers. An average 76.8% were direct admissions. More than half (58%) of the 209 trauma centers that responded to the ownership question were private not-for-profit organizations. About half (45%) of the centers had more than three resuscitation bays. Level I centers had an average of 3.4 resuscitation bays, compared with an average of 2.4 resuscitation bays dedicated to trauma in Level II centers.

Availability of Trauma Personnel

Half of the responding trauma centers had OC-attending level trauma surgeons, and the other half IH (Table 3). One-third (37%) of the centers did not have surgical residents available for trauma care. The specialty surgeons (neuro, orthopedic, and facial/maxillary surgeons) were available through the OC system in the majority of trauma centers.

The ACS-designated centers had significantly more IH-attending level surgeons and anesthesiologists than did the
state-designated centers (Table 4). Also, IH neurosurgeons and orthopedic surgeons, as well as trauma surgeons and anesthesiologists were present significantly more in Level I trauma centers than in Level II centers.

Regardless of the availability of surgical residents, 100% of the trauma centers with an IH system indicated that trauma surgeons were physically present at the bedside within 15 minutes for trauma service. However, among trauma centers

<table>
<thead>
<tr>
<th>State</th>
<th>Number of Trauma Centers Identified</th>
<th>Number of Trauma Centers Mailed</th>
<th>Number (%) of Trauma Centers Including Responses of Trauma Directors</th>
<th>Number (%) of Trauma Centers Including Responses of Trauma Coordinators</th>
</tr>
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<td>Arkansas</td>
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<td>Wyoming</td>
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<td>7</td>
<td>5 (71)</td>
<td>5 (71)</td>
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<tr>
<td>Total</td>
<td>457</td>
<td>450</td>
<td>254 (56)</td>
<td>218 (48)</td>
</tr>
</tbody>
</table>

N/A, not applicable.
The centers with an IH system (60%) had a trauma surgeon available at the time of patient admission significantly more than centers with an OC system did (22%). Sixty-six percent of the trauma centers responded that the anesthesiologists were available within 5 minutes when they were requested for anesthesia. Table 7 compares availability of trauma specialists within 15 minutes by trauma center level, designation type, and trauma admission volume. Level I trauma centers were significantly more likely to have a trauma surgeon present within 15 minutes of patient’s admission than were Level II centers (p < 0.03). Likewise, ACS-designated centers were more likely to have a trauma surgeon present within 15 minutes than were state-designated centers (p < 0.001).

### DISCUSSION

#### IH Versus OC Trauma Coverage

Little prior data exists on the availability of trauma specialists at centers with either IH or OC systems. Published studies have not demonstrated consistent advantages of an IH system for trauma surgeons. One retrospective review study concluded that there were no differences in time to operating room entry or mortality for those in need of urgent surgery between centers with IH or OC systems. Demarest et al. reported a prospective study comparing IH versus OC coverage of attending trauma surgeons at comparable Level I trauma centers and found no significant differences between the two systems in time to provision of clinical care nor in mortality rates, although the study did not control for the effect of significant patient population differences with respect to age, injury severity, and Glasgow Coma Scale score. In another study, the mean response time of trauma surgeons was significantly more rapid for the IH centers (4 minutes) than for the OC centers (15 minutes) after controlling for injury severity. This study, however, did not differentiate response to call versus physical presence at the bedside.

A comparison of two trauma systems with similar patient population and within the same geographic area showed that the presence of a trauma surgeon on the trauma team reduced resuscitation time,2 which was shown to be an important factor in the patient’s eventual outcome. In addition, centers with IH-attending surgeon coverage had reduced time from patient admission to operating room incision for penetrating trauma, reduced cost, reduced time to diagnostic testing, therapeutic intervention, and reduced time to the operating room after the initial resuscitation of patients with severe injury.

The survey results reported here show a large variability among centers with IH versus OC systems for different specialties. For emergency medicine, attending-level IH coverage was nearly universal (99%), versus 46% for trauma surgery. Even with IH systems, the time to the physical presence of trauma specialists varied. The centers with IH systems (60%) had a trauma surgeon at the time of patient admission significantly more than did centers with an OC system (22%).

### Table 2 Characteristics of Trauma Centers*

<table>
<thead>
<tr>
<th>Ownership, n (%)</th>
<th>Public 70 (33.5)</th>
<th>Private for profit 17 (8.1)</th>
<th>Private not for profit 122 (58.4)</th>
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</thead>
<tbody>
<tr>
<td>Trauma center level, n (%)</td>
<td>Level I 89 (43.4)</td>
<td>Level II 116 (56.6)</td>
<td></td>
</tr>
<tr>
<td>Designation of trauma center level, n (%)</td>
<td>American College of Surgeon (ACS) 67 (31.6)</td>
<td>State 139 (65.6)</td>
<td>Other 6 (2.8)</td>
</tr>
<tr>
<td>Number of resuscitation bays for trauma care, n (%)</td>
<td>≤2 116 (54.7)</td>
<td>3–5 81 (38.2)</td>
<td>≥6 15 (7.1)</td>
</tr>
<tr>
<td>Number of beds, n (%)</td>
<td>&lt;100 8 (4.0)</td>
<td>100–299 38 (18.8)</td>
<td>300–499 86 (42.6)</td>
</tr>
<tr>
<td>Number of trauma admissions in the last fiscal year, n (%)</td>
<td>&lt;500 40 (21.0)</td>
<td>500–1,000 59 (30.9)</td>
<td>1,001–2,000 65 (34.0)</td>
</tr>
<tr>
<td>Of total trauma admissions, mean (SD)</td>
<td>Percentage of direct admissions 76.82 (25.38)</td>
<td>Percentage of transfer 22.62 (24.65)</td>
<td></td>
</tr>
<tr>
<td>Of total trauma admissions, mean (SD)</td>
<td>Percentage of high severity/priority 34.39 (21.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of personnel in trauma unit, mean (SD)</td>
<td>Full-time Resident/Fellow 7.17 (35.26)</td>
<td>Full-time MDs 8.22 (19.05)</td>
<td>Part-time MDs 4.54 (15.67)</td>
</tr>
<tr>
<td>Consultant MDs 13.40 (29.80)</td>
<td>Full-time RNs 27.65 (72.04)</td>
<td>Part-time RNs 78 (9.97)</td>
<td>Full-time RNs working in a trauma unit over 2 yr 24.59 (11.97)</td>
</tr>
</tbody>
</table>

* Based on responses of trauma coordinator survey.

with an OC system, 83% of centers that had surgical residents available reported that trauma-attending surgeons were present within 15 minutes, compared with 68% of centers that had no surgical residents available.

The composition of the trauma team was designated by a formal protocol in almost all trauma centers (Table 5). However, in 64% of both Level I and Level II trauma centers, anesthesiologists were required by protocol, and in 36%, their presence was determined by judgment of needs.

### Presence of Trauma Specialists in the Hypothetical Scenario

The trauma surgeon was available within 5 minutes after patient arrival at a trauma center in 52% of the responding centers (Table 6). The centers with an IH system (60%) had a trauma surgeon available at the time of patient admission significantly more than centers with an OC system did (22%).

The survey results reported here show a large variability among centers with IH versus OC systems for different specialties. For emergency medicine, attending-level IH coverage was nearly universal (99%), versus 46% for trauma surgery. Even with IH systems, the time to the physical presence of trauma specialists varied. The centers with IH systems (60%) had a trauma surgeon at the time of patient admission significantly more than did centers with an OC system (22%).
According to Donabedian’s quality of care model, a good structure increases the likelihood of good processes, and good processes increase the likelihood of good outcomes. Although previous studies comparing OC and IH systems (structure) did not demonstrate consistent differences in outcomes, many have suggested the importance of trauma surgeons’ availability within 15 minutes of patient’s arrival (processes), regardless of which systems were used. For example, Demarest et al. suggested that the ability of centers with OC systems to provide clinical care with a mortality rate similar to centers with IH systems was accomplished when OC trauma attending surgeons were present at the trauma center within 15 minutes. For another example, Fulda et al. suggested that there was no difference in mortality among patients when managed by centers with IH and OC trauma surgeons when they were both available within 15 minutes.

Our study examined the relationship between structure (IH vs. OC, Level I vs. II, ACS designation vs. state designation) and processes (trauma surgeon availability with 15 minutes of an admission). Although 82% of the Level I and II centers reported that a trauma surgeon was present within 15 minutes of patient arrival, all centers with IH systems had trauma surgeons present within 15 minutes, versus 76% by centers with OC systems.

The OC system may be cost-effective for low-volume trauma centers. In a teaching institution, an OC system for the attending surgeon with immediate availability of senior-level trauma surgeons may be a viable option. However, further research is needed to determine the optimal model for providing trauma care in various settings.

Table 3 Availability of Personnel for Trauma Services, n (%)

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Not Available to Trauma Services</th>
<th>On-Call</th>
<th>In-House</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;30 min</td>
<td>≤30 min</td>
<td>Covering Trauma and Nontrauma Services</td>
</tr>
<tr>
<td>Trauma surgeon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attending</td>
<td>—</td>
<td>5 (2.4)</td>
<td>109 (51.6)</td>
</tr>
<tr>
<td>Fellow</td>
<td>118 (81.3)</td>
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<td>1 (0.7)</td>
</tr>
<tr>
<td>Residents</td>
<td>66 (37.1)</td>
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<td>3 (1.7)</td>
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<tr>
<td>Anesthesiologist</td>
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</tr>
<tr>
<td>Attending</td>
<td>—</td>
<td>2 (0.9)</td>
<td>56 (26.7)</td>
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<tr>
<td>Residents</td>
<td>95 (61.7)</td>
<td>1 (0.5)</td>
<td>19 (10.2)</td>
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<td>CRNA</td>
<td>54 (28.9)</td>
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</tr>
<tr>
<td>Attending</td>
<td>—</td>
<td>—</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Residents</td>
<td>77 (47.5)</td>
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<td>Radiology technician</td>
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<td>5 (2.3)</td>
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<td>Respiratory therapist</td>
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<td>Trauma technician</td>
<td>51 (27.3)</td>
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<tr>
<td>Specialty surgeon</td>
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<tr>
<td>Neurosurgeon</td>
<td>10 (4.8)</td>
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<td>134 (63.8)</td>
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<tr>
<td>Orthopedic surgeon</td>
<td>1 (0.5)</td>
<td>19 (9.0)</td>
<td>140 (66.3)</td>
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<td>Plastic surgeon</td>
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<td>44 (20.8)</td>
<td>127 (60.2)</td>
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<tr>
<td>Faciomaxillary surgeon</td>
<td>8 (3.8)</td>
<td>47 (22.4)</td>
<td>128 (60.9)</td>
</tr>
<tr>
<td>Ophthalmology surgeon</td>
<td>6 (2.9)</td>
<td>56 (26.9)</td>
<td>125 (60.1)</td>
</tr>
</tbody>
</table>

Table 4 Comparisons of Trauma Centers With In-House System, n (%)

<table>
<thead>
<tr>
<th>In-House Trauma Physicians (Attending)</th>
<th>Designation Type</th>
<th>Trauma Center Level</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACS State</td>
<td>Level I</td>
<td>Level II</td>
</tr>
<tr>
<td>Trauma surgeon</td>
<td>37 (55.2)</td>
<td>60 (67.4)</td>
<td>35 (30.4)</td>
</tr>
<tr>
<td>Anesthesiologist</td>
<td>56 (84.8)</td>
<td>85 (96.6)</td>
<td>64 (56.1)</td>
</tr>
<tr>
<td>Emergency physician</td>
<td>65 (98.5)</td>
<td>87 (100)</td>
<td>112 (98.2)</td>
</tr>
<tr>
<td>Neurosurgeon</td>
<td>18 (26.9)</td>
<td>37 (41.6)</td>
<td>8 (7.0)</td>
</tr>
<tr>
<td>Orthopedic surgeon</td>
<td>17 (25.4)</td>
<td>41 (46.6)</td>
<td>9 (7.8)</td>
</tr>
<tr>
<td>NS, not significant.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Structures and Processes of Trauma Care

According to Donabedian’s quality of care model, a good structure increases the likelihood of good processes, and good processes increase the likelihood of good outcomes. Although previous studies comparing OC and IH systems (structure) did not demonstrate consistent differences in outcomes, many have suggested the importance of trauma surgeons’ availability within 15 minutes of patient’s arrival (processes), regardless of which systems were used. For example, Demarest et al. suggested that the ability of centers with OC systems to provide clinical care with a mortality rate similar to centers with IH systems was accomplished when OC trauma attending surgeons were present at the trauma center within 15 minutes. For another example, Fulda et al. suggested that there was no difference in mortality among patients when managed by centers with IH and OC trauma surgeons when they were both available within 15 minutes. Our study examined the relationship between structure (IH vs. OC, Level I vs. II, ACS designation vs. state designation) and processes (trauma surgeon availability with 15 minutes of an admission). Although 82% of the Level I and II centers reported that a trauma surgeon was present within 15 minutes of patient arrival, all centers with IH systems had trauma surgeons present within 15 minutes of patient admission, versus 76% by centers with OC systems.

The OC system may be cost-effective for low-volume trauma centers. In a teaching institution, an OC system for the attending surgeon with immediate availability of senior-level trauma surgeons may be a viable option. However, further research is needed to determine the optimal model for providing trauma care in various settings.
surgical residents may be useful to provide financial savings.\(^3\)
For optimal trauma care, whether an IH system is preferred over an OC system or vice versa may not be a key concern, as long as the trauma surgeon is available within the optimal time period. For patients with severe injury, they should be available upon patient’s arrival.

The ACSCOT requires the attending surgeon’s immediate presence in the management of patients with injury for resuscitation, operative procedures, and therapeutic decisions.\(^1\) They have defined that this involvement should be achieved by availability of an IH attending surgeon 24 hours a day, 7 days a week.\(^1\) In our survey, the IH attending surgeon system was available in 56.5% of the trauma centers designated by ACS, versus 38.5% of trauma centers designated by state. Additionally, trauma surgeons were significantly more likely to be present within 15 minutes of an admission of a hypothetical patient with high-severity injury in ACS-designated centers (98%) than in state-designated centers (80%). Previous studies have shown the positive influence of the ACS designation on hospital performance and patient outcomes.\(^10–12\)

Neurosurgeons were mostly available through the OC system. However, an unexpected finding was that 1.1% of the Level I and 4.3% of Level II trauma centers had no neurosurgeons available at all, even though the guidelines of ACSCOT\(^1\) recommended a reliable OC schedule to provide neurotrauma care. A number of models for the back-up call schedule may be acceptable based on the number of neurosurgeons available in the region, number of neurosurgical procedures performed annually at the trauma centers, or a residency program.\(^1\) The chief neurosurgery resident may serve as the first backup in centers with neurosurgical services. In communities where the number of neurosurgeons is limited, at least a single trauma center should be designated for neurosurgical services with a transfer agreement among the trauma centers in the community.\(^1\) Also, ACSCOT documented that a back-up schedule is necessary in centers where more than 25 emergency neurosurgical procedures, excluding intracranial pressure monitors, are performed within 24 hours of admission per year.\(^1\) Given the volume of neurotrauma patients, neurosurgical manpower, and timeliness of head injury, Esposito et al.\(^13\) suggested that immediate availability of a neurosurgeon is not essential if a properly trained and accredited trauma surgeon or other clinicians can evaluate and monitor patients with neurologic injury. Trauma surgeons can perform burr holes and craniotomies when needed emergently.\(^13\) The management of severe head injury by general surgeons may be the best option in a circumstance in which specialized neurosurgical services are limited and emergency referrals are impractical.\(^14\)

Early decompression of intracranial hematomas in the emergency room were suggested to prevent further damage to the brain.\(^15\) However, an attending neurosurgeon must be promptly available when further neurosurgical consultation is needed in Level I and II trauma centers.\(^1\)

### Table 6 Timely Presence of Expert Needed for Scenario: A Patient With High Severity Injury, n (%)

<table>
<thead>
<tr>
<th>At Patient Arrival</th>
<th>&lt;5 min</th>
<th>&lt;15 min</th>
<th>&lt;30 min</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma surgeon</td>
<td>94 (37.3)</td>
<td>38 (15.1)</td>
<td>74 (29.4)</td>
<td>45 (17.8)</td>
</tr>
<tr>
<td>Emergency medicine physician</td>
<td>236 (94.0)</td>
<td>7 (2.8)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Anesthesiologist</td>
<td>72 (29.0)</td>
<td>92 (37.1)</td>
<td>47 (18.9)</td>
<td>29 (11.7)</td>
</tr>
<tr>
<td>Emergency medicine technician</td>
<td>156 (67.2)</td>
<td>24 (10.3)</td>
<td>6 (2.6)</td>
<td>—</td>
</tr>
<tr>
<td>Respiratory therapist</td>
<td>157 (62.5)</td>
<td>84 (33.5)</td>
<td>8 (3.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Radiology technician</td>
<td>167 (66.5)</td>
<td>72 (28.7)</td>
<td>6 (2.4)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Nurse</td>
<td>239 (95.6)</td>
<td>8 (3.2)</td>
<td>2 (0.8)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

NA, not applicable.

### Table 7 Comparisons of Presence of Expert Needed for Scenario: High Severity Injury

<table>
<thead>
<tr>
<th>Presence Within 15 min, n (%)</th>
<th>Trauma Surgeon</th>
<th>p</th>
<th>EM Physician</th>
<th>p</th>
<th>Anesthesiologist</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma center level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level I</td>
<td>71 (93.4)</td>
<td>0.037</td>
<td>71 (100)</td>
<td>NS</td>
<td>71 (98.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Level II</td>
<td>75 (81.5)</td>
<td></td>
<td>91 (98.9)</td>
<td></td>
<td>75 (83.3)</td>
<td></td>
</tr>
<tr>
<td>Designation type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>53 (98.1)</td>
<td>0.001</td>
<td>51 (100)</td>
<td>NS</td>
<td>47 (94.0)</td>
<td>NS</td>
</tr>
<tr>
<td>State</td>
<td>94 (80.3)</td>
<td></td>
<td>114 (99.1)</td>
<td></td>
<td>99 (86.8)</td>
<td></td>
</tr>
<tr>
<td>Number of trauma admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>20 (66.7)</td>
<td>0.003</td>
<td>29 (96.7)</td>
<td>NS</td>
<td>23 (76.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>500–1,000</td>
<td>43 (87.8)</td>
<td></td>
<td>49 (100)</td>
<td></td>
<td>40 (87.0)</td>
<td></td>
</tr>
<tr>
<td>1,001–2,000</td>
<td>50 (89.3)</td>
<td></td>
<td>54 (100)</td>
<td></td>
<td>53 (96.4)</td>
<td></td>
</tr>
<tr>
<td>&gt;2,000</td>
<td>24 (100)</td>
<td></td>
<td>21 (100)</td>
<td></td>
<td>21 (100)</td>
<td></td>
</tr>
</tbody>
</table>

NS, not significant.
Variability of Availability of Trauma Surgeons Versus Emergency Medicine

Discussions of OC versus IH systems for accessing the expertise of trauma surgeons may have ignored an important aspect of physician availability across Level I and II trauma centers. When compared with trauma surgeons, emergency medicine physicians were significantly more likely to be present at the time of patient’s arrival (94% vs. 37%). Furthermore, nearly all (97%) of the centers with 500 or less annual admissions reported the presence of an emergency medicine physician within 15 minutes of a hypothetical high-severity admission, whereas all high-volume centers with more than 2,000 annual admissions reported the availability of trauma surgeons. Ideally, trauma surgeons should be present 100% of the time at a patient’s arrival to coordinate the resuscitation and diagnostic studies when a patient needs immediate surgery. However, in low-volume trauma centers, it may require unrealistic resources to have trauma surgeons present all the time. For those centers with less than 2,000 annual admissions (86% of the responding centers), early triage, better notification and transfer systems, perhaps based on advanced telecommunication technology such as image and data transfer, and compensation for IH call may be a solution to better use of the trauma surgical specialties. Secondary triage strategies should also be explored to identify those trauma patients who require the unique expertise of a trauma surgeon during the initial phase of trauma management. For centers with low patient volume where trauma surgeons are not present 100% of the time, using telecommunication technology may allow these trauma surgeons to contribute their recommendations to the initial management by emergency medicine physicians at the right time with their special skills. However, an earlier article on the results of the survey study indicates a paucity of use of advanced telecommunication technologies.

One of our study limitations is that the findings were derived from the perception of trauma directors, not from objective measurement. Particularly, trauma directors were asked the time it took for trauma expertise to arrive at the patient bedside in the hypothetical scenario. There may be a gap between the perceived arrival time and actually observed time. However, a strength of our study is that the cross-sectional survey methodology allowed us to reach as many trauma centers as possible and to receive general information regarding the availability of trauma expertise in Level I and II trauma centers across the nation. Another limitation is that this study did not investigate specifically whether the first responding clinician for new patients needing surgery was a resident or an attending-level surgeon. Senior residents may be the first surgical contact for patients who need specific surgical consultation, and these residents may be considered the “trauma surgeon” in many teaching trauma centers. Further research should include this clarification to allow for more insight regarding responding surgeons.

The last limitation is that this study did not survey what benefits were provided for IH call or OC trauma surgical specialties. The compensation for IH call may affect the timely presence of trauma specialties.

Our survey study quantified the current availability of trauma specialists among a representative sample of all Level I and II trauma centers in the United States. Despite ACS and state designation, there was a large variation in the clinical expertise available at or shortly after admission of a trauma patient. IH coverage was associated with more readily available trauma specialists within 15 minutes of patient admission. Although it may be desirable to have IH trauma specialists in all trauma centers, in reality, emergency medicine physicians are often the only available physicians during initial resuscitation, especially in centers with low patient volume. Devising technologic systems (e.g., telemedicine) to monitor patients en route or before admission and to coordinate trauma teams may be the best way to overcome the variability and limitation in availability of trauma specialists on arrival of patients with trauma in Level I and II trauma centers.

ACKNOWLEDGMENTS

We thank the trauma directors and coordinators who responded to the survey.

REFERENCES


Hepatic Vascular Isolation in Treatment of a Complex Hepatic Vein Injury

João Eduardo Nicoluzzi, MD, Luís Carlos Von Bahten, MD, and Gerson Laux, MD

Injuries to the main hepatic veins (juxtahepatic venous injuries) have a very high mortality rate, regardless of the technique used for repair. Isolated reports of survivors have, for the most part, been managed by vascular isolation techniques, usually with an atriocaval shunt. In 1986, a report by Pachter et al. described 15 out of 66 patients surviving the procedure over a 15-year period. The high mortality resulted from multiple factors, including delay in the diagnosis of the juxtahepatic venous injury, lack of familiarity of the technique for atriocaval shunting, and using the shunt as a last resort when other maneuvers had failed. Atriocaval shunting has a mortality rate of 90% at some institutions, and other techniques often fail because of the massive hemorrhage associated with hepatic vein injuries.

The continued high mortality associated with hepatic vein and retrohepatic caval injuries has led to a variety of therapeutic suggestions. These techniques include intraparenchymal or perihepatic packing, lobar resection, deep hepatic suture, and direct suture repair of the bleeding vessels. However, these have resulted in mortality rates of 50 to 89% for penetrating wounds, and >90 to 100% for blunt trauma.

Nonoperative management of blunt hepatic injuries has been firmly established as the preferred treatment modality. It would appear that anywhere from 47 to 82% of all blunt adult hepatic injuries can be managed nonoperatively with a success rate of over 95%. Recent reports, however, have documented that patients with grade IV and V injuries constituted 21 to 33% of all patients with blunt hepatic injuries managed nonoperatively. The precise criteria for including a patient in the nonoperative track remains controversial. Hemodynamic stability, however, has become universally accepted as the single most important inclusion criterion, and in some instances as the only criterion, for managing patients with blunt hepatic injuries nonoperatively. The presence of extravasation of contrast material (“pooling of contrast”) on a computed tomography scan even in the presence of hemodynamic stability mandates further action.

Several vascular exclusion procedures have been proposed to facilitate the repair of the retrohepatic vena cava and major hepatic veins by limiting blood flow through the injured area. The great majority of therapeutic recommendations have been derived from retrospective studies of small numbers of patients, and, even in the clinical reports proposing technical solutions to the problem, deaths usually outnumber survivors.

We report a case of diagnosis and management of a severe hepatic vein injury using hepatic vascular exclusion (HVE) without aortic clamping.

CASE REPORT

A 27-year-old man sustained a stab wound injury on the right flank. Upon arrival at the hospital 20 to 25 minutes after injury, he was awake and alert. He had a systolic blood pressure of 110 mm Hg and was complaining of abdominal pain. Laparotomy revealed a laceration approximately 10-cm deep between hepatic segments V and VI. Partial hemorrhage control was obtained with manual compression and portal triad occlusion, but bleeding continued despite these maneuvers. As the patient was stable and blood salvage available, a decision was made to proceed with HVE and to attempt repair. To compensate for the consequences of blood pooling in the lower half of the body during HVE, an increase of fluid infusion was performed before HVE to obtain a slight volume overloading. Clamp were then serially placed on the porta hepatis, infrahepatic suprarenal inferior vena cava (IVC), and suprahepatic IVC for 3 minutes to test the hemodynamic tolerance to HVE after which they were released. As the HVE was well tolerated, a few minutes later clamps were applied again. Hepatotomy was then performed disclosing a large tear on the right hepatic vein. The injury was repaired and the liver was left opened without omentum packing (Fig. 1). The clamps were removed in the reverse order of their application. No venous shunt or refrigeration was used. The amount of blood transfusion administered was 650 mL. The patient initially presented a low output biliary fistula, being discharged from the hospital fully recovered after 2 weeks.
DISCUSSION

The management of hepatic vein injuries is complex and controversial, with most patients dying regardless of the technique used for repair. Although hepatic packing is occasionally successful, it often fails when the injury extends directly into the vena cava. It is known that packing a juxtahepatic caval or major hepatic vein injury may produce permanent occlusion without rebleeding. Presumably when this occurs, the low-pressure system seals with fibrin and subsequently heals. Attempts at suture repair usually worsen the injury and extend the laceration. The use of an atriocaval shunt is extremely controversial despite reports of survival rates of 33% when used early. Most trauma centers have been unable to duplicate these good results.

We have described the case of a severe intraparenchymal juxtahepatic vein injury. We believe that HVE without aortic cross-clamp can be a very useful technique that could be added to the armamentarium of the trauma surgeon, albeit to a very limited number of patients. The advantage of using this technique is to create a bloodless field with perfect hemorrhage control.

Surgeons have seldom cross-clamped the IVC above the liver in elective operations. The abrupt interruption of this vessel, which normally carries two thirds of the cardiac output back to the heart, is usually considered to be very poorly tolerated and leads to cardiovascular collapse. This fear has made associated aortic cross-clamp become a routine whenever HVE is used. However, when the aortic cross-clamp is applied, arrhythmias are a problem, presumably because of the added afterload. Removal of the aortic cross-clamp is also associated to hypotension as a result of several postulated mechanisms. However, more recent experience has shown that such aortic clamping during HVE is not mandatory. As opposed to what has been observed in dogs and pigs, no cardiovascular collapse occurs after occlusion of the suprahepatic IVC in most patients. The difference between man and other animals may be explained by the presence of the large collateral venous channels in humans, such as theazygos vein. A similar tolerance to suprahepatic IVC clamping has been reported in patients after receiving liver transplantation. We believe that HVE, without associated aortic cross-clamp, can be applied in trauma depending mainly on the lack of intravascular volume depletion. The main reason for the successful outcome of our patient was his previous hemodynamic stability, which allowed for the safe application of the HVE and clearly influenced his tolerance to the procedure.

HVE can be applied to patients with severe venous injury. To avoid the effects of the aortic cross-clamp, this technique must be limited to patients who have not suffered severe intravascular volume depletion, because it tends to cause cardiac arrest in severely hypovolemic patients.

REFERENCES


Laparoscopic Splenectomy for Delayed Splenic Rupture After Embolization

Edward Pucci, DO, Fred Brody, MD, FACS, MBA, Harry Zemon, MD, Todd Ponsky, MD, and Anthony Venbrux, MD

Splenectomy remains the most common indication for laparotomy after blunt trauma. Historically, these injuries were managed with laparotomy and splenectomy. However, the risk of overwhelming postsplenectomy sepsis (OPSS) after splenectomy is 0.026% and 0.8% in adults and children, respectively. The estimated mortality of OPSS is between 50% and 70%. Based on the risk of OPSS, Christo introduced partial splenectomy and splenorrhapy in 1962 for blunt and penetrating trauma. Since then, splenic preservation and splenorrhaphy are initially attempted at the time of surgery.

Nonoperative management of splenic trauma began in the 1980s in pediatric patients. This management protocol was extremely successful for this cohort. However, early reports of nonoperative management in adults documented failure rates as high as 70%. Since the 1990s, management protocols and technological improvements in computed tomography (CT) have made nonoperative management the standard of care for blunt splenic trauma. Currently, nonoperative management of splenic trauma includes splenic artery embolization. At this time, several large series report the success of splenic artery embolization for traumatic injuries. However, splenic embolization can fail and certain injuries are not amenable to embolization. In these scenarios, usually grade IV and V injuries, splenectomy remains the definitive treatment.

For benign and malignant disease, laparoscopic splenectomy is effective and the preferred approach for most patients. Yet splenic trauma may be considered a contraindication for laparoscopy. Nevertheless, the literature documents a few cases of laparoscopic splenectomy for trauma. Basso et al. reported the first totally laparoscopic splenectomy for a ruptured spleen in 2003. We report the first case of a totally laparoscopic splenectomy for delayed splenic rupture after embolization.

CASE REPORT

A 32-year-old male bicyclist was admitted to the hospital after he was struck by a bus. On presentation, he was hemodynamically stable with a Glasgow Coma Scale (GCS) score of 15 and reported no loss of consciousness. He complained of pain in his left shoulder and left lower extremities. His physical examination revealed abrasions around his left shoulder, left upper extremity, and along the left flank. He was tender along his cervical spine and below his left scapula. Laboratory work showed a hematocrit of 42.3 mg/dL. Chest and cervical spine X-rays were normal. CT scans of his head and cervical spine were normal as well. Based on his mechanism of injury and continued pain, the patient was admitted for observation.

Overnight, the patient had an isolated episode of hypotension with a blood pressure measurement of 74/55 mm Hg. He was given one liter of lactated ringers and his blood pressure responded, rising to 110/70 mm Hg. The next morning, the patient complained of mild abdominal pain with nausea. His hematocrit at that time was 29.0 mg/dL. A CT scan of the abdomen and pelvis showed a hemoperitoneum with a large splenic laceration (Fig. 1). The patient was then sent to interventional radiology and underwent a celiac angiogram. At angiography, extravasation of contrast was documented from a segmental branch from the lower pole of the spleen (Fig. 2). The extravasation pattern was consistent with a false aneurysm. The aneurysm was embolized with three titanium coils (Fig. 3).

After embolization, the patient was monitored in the intensive care unit. His hematocrit drifted to 17.1 mg/dL on postprocedure day two. He was transfused 2 units of packed red blood cells. The patient remained stable until postprocedure day four, when he developed acute, right lower quadrant pain with abdominal distension. Concurrently, his systolic blood pressure fell to 84 mm Hg. He was taken to the operating room emergently.
The patient was positioned in a modified, right lateral decubitus position at 30 degrees. A 10-mm Visiport (USSC, Norwalk, CT) was used to gain access below the costal margin. A 12-mm port and two 5-mm ports were placed along the subcostal margin. Initially, a large hemoperitoneum was apparent once the pneumoperitoneum was established (Fig. 4). Approximately 1.5 L of blood was aspirated and a large amount of omentum was adherent to the spleen. This was left intact and the patient was rotated supine. A diagnostic laparoscopy was performed and no other visceral injuries were ascertained within the liver, small intestine, or colon. The patient was rotated to a 90-degree decubitus position and the omentum was peeled off of the spleen. A large intraparenchymal laceration was seen with almost-complete avulsion of half of the spleen (Fig. 5). A gauze pad was inserted to tamponade the laceration. The short gastric and avascular attachments were divided with the harmonic scalpel. The splenic hilum was then divided with two firings of a 2.5-mm stapler. The spleen was placed into a prolene bag, morsilized, and removed through the 12-mm port. The anterior and posterior surfaces of the stomach were inspected as well. A 10-mm drain was left in the left upper quadrant near the pancreas. The drain was placed due to the proximity of the pancreatic tail to the splenic hilum and the mechanism of

Fig. 1. Initial CT scan of the abdomen documenting the parenchymal hematoma. No extravasation of contrast is noted along the splenic artery or within the hilum.

Fig. 2. Celiac angiogram demonstrating extravasation of contrast from a terminal segmental branch within the lower pole of the spleen.

Fig. 3. Celiac angiogram after successful embolization with three titanium coils.

Fig. 4. Initial diagnostic laparoscopy discovered a large hemoperitoneum.
injury. Postoperatively, the patient remained stable with a hematocrit of 29.6 mg/dL. His postoperative ileus resolved by day three and he was tolerating a regular diet by postoperative day four. He was discharged to home on postoperative day six. He returned to work and his normal physical activities three weeks postoperatively.

**DISCUSSION**

Nonoperative management of blunt splenic trauma is the gold standard for hemodynamically stable patients. Peritonitis, associated injuries requiring surgery, overall severity of injuries, evidence of hypovolemic shock, and age are the primary factors that may dictate nonoperative versus operative management of blunt splenic injuries. These signs and symptoms are usually apparent at the time of presentation. However, delayed splenic rupture may necessitate surgical intervention even after stabilizing a patient for several days. Delayed splenic rupture may be caused by gradual enlargement of a false aneurysm or hematoma, with eventual rupture into the peritoneal cavity or lesser sac. This scenario was clearly apparent in our patient. Based on the splenic injury scoring system from the American Association for the Surgery of Trauma (Table 1), our patient had a grade III injury because of the subcapsular hematoma that was greater than 50%, the intraparenchymal hematoma that was larger than 2 cm, and the 3-cm laceration through the parenchyma.

Since the 1990s, management protocols and sophisticated radiologic studies have evolved to make nonoperative management the standard of care. In 1995, Schurr noted a 13% failure rate and reported that two-thirds of the observed failures were associated with a vascular blush on CT. Subsequently, Davis showed a failure rate of only 5% using an angiographic embolization protocol. In their protocol, patients who presented with vascular blushes identified on CT underwent splenic embolization.

Depending on the institution’s or surgeon’s protocol, nonoperative management may or may not include blood transfusions. Reactions from blood transfusions can cause serious complications, including death. With the introduction of donor screening, the risk of post-transfusion hepatitis has fallen to less than 1%. Meanwhile, transfusions can suppress the recipient’s immune response. This is well documented in the literature regarding renal transplantation and oncologic surgery. Moreover, the risk of human immunodeficiency virus is estimated at 1:2,000,000 to 1:200,000 per unit of red blood cells. Although these values are exceedingly low, they must be considered in each patient’s clinical algorithm.

Several management issues were identified during the care of this patient. When the patient’s hemoglobin decreased to 17 mg/dL 2 days after splenic embolization, operative intervention or repeat angiography may have been acceptable options. However, nonoperative management continued with monitoring in the intensive care unit and serial examinations. An earlier CT scan of the abdomen and pelvis (at presentation to the emergency room) may have identified the patient’s lesion earlier. However, this would not have altered his clinical management. The patient still would have undergone nonoperative management for his blunt trauma. Again, many surgeons would have pursued operative intervention with a hemoglobin of 17 mg/dL, and our management algorithm may have pushed the clinical limits of nonoperative treatment. Yet, the age of embolization and laparoscopy may engender a new protocol for the management of blunt splenic injury.

Positioning the patient in a semilateral 30-degree position made it possible to go from a supine to a lateral decubitus position by simply rotating the table. This position enabled a thorough diagnostic laparoscopy before the splenectomy. This position also enables conversion to an open procedure if

**Table 1 American Association for the Surgery of Trauma Splenic Injury Scoring System**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Type of Injury</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hematoma</td>
<td>&lt;10% of surface area</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>&lt;1-cm depth</td>
</tr>
<tr>
<td>II</td>
<td>Hematoma</td>
<td>10% to 50% surface area; &lt;5-cm diameter</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>1- to 3-cm depth</td>
</tr>
<tr>
<td>III</td>
<td>Hematoma</td>
<td>&gt;50% surface area; ruptured hematoma with bleeding, parenchymal hematoma &gt;2 cm or expanding</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>&gt;3 cm or involving trabecular vessels</td>
</tr>
<tr>
<td>IV</td>
<td>Laceration</td>
<td>Segmental or hilar vessels with devascularization of 25% spleen</td>
</tr>
<tr>
<td>V</td>
<td>Laceration</td>
<td>Completely fractured</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Hilar injury with necrotic spleen</td>
</tr>
</tbody>
</table>

**Fig. 5.** Significant laceration and avulsion of the lower pole of the spleen.
necessary. Technically, four ports, as opposed to the standard three ports, were used. Two ports were used for dissection and the third port was used for a suction/irrigator. The suction was essential to remove the hemoperitoneum. Obviously, the fourth port was for the laparoscope.

Diagnostic and therapeutic laparoscopy are now surgical options for blunt and penetrating injuries. Concurrently, laparoscopic surgical skills have improved significantly during the last 10 years and more complex abdominal surgeries are performed laparoscopically. As a result, laparoscopic splenectomy may one day be the standard of care for splenic rupture. Although a laparoscopic approach was successful for this patient, the majority of trauma surgeons in the United States may not be prepared to embrace this treatment plan at this time. However, laparoscopy is a useful adjunct for many trauma patients, but its exact role has not been delineated.

REFERENCES

Gunshot Abdominal Wall Injury Reconstructed with an Innervated Latissimus Dorsi Free Flap

Pedro Ferreira, MD, Edgardo Malheiro, MD, Miguel Choupina, MD, Carlos Pinho, MD, Rui Barbosa, MD, Jorge Reis, MD, and José Amarante, MD, PhD

Loss of abdominal wall integrity can occur after trauma, infection, or surgical resection. The components involved in abdominal wall wounds include skin, muscle, or fascia alone, as well as any combination of these. This article presents the case of a 33-year-old woman who suffered a severe abdominal wall injury by a gunshot. After stabilization of the systemic and local conditions, a tensor fascia latae flap and rectus abdominis muscle flaps and a split-thickness skin graft were used to achieve abdominal wall closure. Definitive reconstruction was made 7 years later with a free innervated latissimus dorsi myocutaneous flap. A literature review about abdominal wall defects reconstruction is also made.

Reconstruction of massive full-thickness defects involving the abdominal wall has always represented a formidable challenge to the reconstructive surgeon. Methods to solve this problem include use of prosthetic mesh, split-thickness skin grafts, the “components separation” technique, tissue expansion, regional flaps, and free flaps.

No single technique can be applied successfully in all types of abdominal wounds. The selection of the reconstructive technique is individualized, based not only on the size of the wound, but also on the specific functional and esthetic requirements of the area and the patient’s general condition.

In situations where skin coverage is adequate but muscle and fascia are not, synthetic materials, particularly polypropylene and expanded polytetrafluoroethylene, have become a common technique for reconstruction. However, they have an increased risk for infection and enteric fistula formation and are relatively contraindicated in contaminated fields. Autogenous reconstruction is advantageous both functionally and cosmetically and is often required in cases of chronic wounds, cases that previous hernia repairs have failed with consequent extruding mesh, or other special anatomic circumstances.

The authors report a clinical case of massive evisceration secondary to a severe gunshot injury, which was primarily reconstructed using a tensor fascia latae flap and rectus abdominis muscle flaps and split-thickness skin graft. During the follow-up, a large hernia measuring 20 × 25 cm became evident in the lower and middle abdomen. Definitive reconstruction was achieved with the microsurgical transfer of an innervated latissimus dorsi myocutaneous free flap.

CASE REPORT

A 33-year-old woman suffered a severe abdominal gunshot injury with multiple small bowel perforations. The patient was treated in a small outlying hospital, where resection of ileum with anastomosis end-to-end was performed; lead foreign bodies were also removed from the abdominal cavity. Debridement of the injured abdominal wall resulted in a massive lower and middle abdominal wall defect, measuring 20 × 25 cm. The patient was sent to our hospital with massive evisceration as a consequence of the abdominal wall defect (Fig. 1). On day 5, after stabilization of the patient’s systemic and local conditions, a tensor fascia latae flap and inferiorly based rectus abdominis muscle flaps were used to cover the exposed viscera (Fig. 2). A split-thickness skin graft was applied over these flaps on day 30. The patient had an uneventful postoperative course and was discharged 50 days after the accident (Fig. 3). The patient was prescribed with an abdominal binder to avoid bulging and to support the abdominal wall, but weakness of the reconstructed wall became obvious and a large hernia measuring 20 × 25 cm was present in the lower and middle abdomen (Fig. 4). Definitive reconstruction of the large abdominal defect was performed 7 years later as decided by the patient. The epithelium of the skin was first dermabraded (Fig. 5), leaving the dermis of the graft as “neoperitoneum.” Thus, the abdominal cavity was not penetrated again. The resultant dermal layer resembled a fascia-like layer of connective tissue and prosthetic mesh was not used. This dermal layer was then covered with an innervated free latissimus dorsi muscle free flap (Fig. 6). The thoracodorsal vessels were anastomosed to the deep circumflex iliac vessels and thoracodorsal nerve was coapted with a

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From the Department of Plastic Reconstructive and Aesthetic Surgery, Hospital de São João, Porto Medical School, Porto, Portugal.
Address for reprints: Pedro Manuel Costa Ferreira, Lugar de Vila-Chã/Carvalhal, 4755-106 Barcelos, Portugal; e-mail: pedro.ferreira@mail.pt.
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muscular branch of the femoralis nerve. The muscle was sutured to the abdominal wall fascia with the appropriate resting tension (Fig. 7).

The postoperative course was uneventful and all surgical sites healed. The patient was discharged on the 12th postoperative day.

No immediate or late complications occurred. The patient continued to wear an abdominal binder for 7 months after definitive reconstruction to prevent stretching of the transplanted latissimus dorsi muscle. Clinical examination 2 years later (Fig. 8) revealed a firm and stable abdominal wall with strong, coordinated contractile function of the free muscle flap. Electromyographic examination demonstrated reinnervation of the latissimus dorsi muscle flap (Fig. 9). The patient reported a subjective increase in abdominal wall strength and significant improvement in the ease of performing activities of daily living.

**DISCUSSION**

Repair of massive full-thickness abdominal wall defects concerning treatment of massive evisceration secondary to trauma, previous surgery, infection, and tumor resection has long been a challenge for the reconstructive surgeon. The goals of abdominal reconstruction are threefold: (1) restoration of function and integrity of the musculofascial abdominal wall, (2) prevention of visceral eventration, and (3) provision of dynamic muscle support.
Treatment for an abdominal defect is selected on basis of several factors, including (1) the medical status of the patient, (2) wound preparedness and depth, and (3) size and position of the defect.

Abdominal trauma from gunshot wound usually requires an exploratory laparotomy for diagnostic and therapeutic purposes. Immediate closure of the abdominal defect is neither feasible nor desirable in many cases, due to intestinal edema, and any attempt to close the abdomen under tension is doomed to fail. A staged reconstruction is recommended after adequate debridement and proper treatment of intra-abdominal injuries. Split-thickness skin grafting to the abdominal viscera is used to achieve a temporary primary closure, but muscular flaps are used less frequently with this intention. Problems such as infection, hernia, and fistulous tract formation are not uncommon complications associated with these treatments. Definitive reconstruction can then be done at a later date, after full stabilization. Several options are available, including various synthetic...
meshes or patches, the “components separation” technique, tissue expansion, pedicled or free musculocutaneous or fasciocutaneous flaps. Each available technique has its own advantages and disadvantages.

The complication rate regarding the use of synthetic mesh is significant, with the most dreaded complications being infection, extrusion, and enterocutaneous fistula formation. Reported by Ramirez et al., the “components separation” technique is useful for midline and central defects. It is not effective for lateral defects or in cases of loss of the rectus abdominis muscles and fascia. This technique is based on enlargement of the abdominal wall surface by translation of the muscular layers. The reherniation rate is relatively high.

Reconstruction with innervated and vascularized myo-fascial composite tissue is ideal and is what abdominal wall expansion attempts to achieve. Skeletal muscle, peripheral nerves, and axial blood vessels can all be effectively expanded. However this is a two-stage procedure that is not used widely. Progressive preoperative pneumoperitoneum as a method of tissue expansion in preparation for the reconstruction of a full-thickness defect of the abdominal wall, has also been reported.

Numerous flaps have been described for abdominal wall closure, including muscle, myocutaneous, fasciocutaneous, pedicled, and free flaps. The role of the tensor fasciae latae as autogenous tissue in reconstruction of abdominal wall defects is well established. Other flaps coming from the thigh were described, such as sartorius, rectus femoris, and anterior thigh fasciocutaneous flap. Disadvantages of these flaps in-

Fig. 7. Immediate postoperative view after definitive abdominal wall reconstruction.

Fig. 8. Appearance of the abdomen 2 years after reconstruction with innervated latissimus dorsi muscle flap.

Fig. 9. Electromyographic results demonstrate muscle reinnervation.
clude limitations in size, limited arc of rotation, and frequent morbidity or functional deficiency at the donor site. The pedicled groin flap,15 rectus abdominis musculocutaneous flap,16 external oblique musculocutaneous flap,17 and extended latissimus dorsi musculocutaneous flap18 were also described for abdominal wall reconstruction.

Although our patient was primarily reconstructed with muscle flaps and no hernia was immediately evident (Fig. 3), tissue laxity occurred with a resultant hernia (Fig. 4). In 1998, Ninkovic et al.19 presented a major advance: the free innervated latissimus dorsi flap as a means to reestablish the contractile force and strength of the lost abdominal wall. These authors reported the use of free latissimus dorsi flap without significant complication in four patients with full thickness defects; two were staged procedures and two were immediate repairs. After that, only few clinical cases were reported using this technique.20,21

Based on this approach, our clinical case reports a massive full-thickness defect of the abdominal wall, reconstructed with a free innervated latissimus dorsi myocutaneous flap.

The advantages of free tissue transfer are well known, and the use of latissimus dorsi musculocutaneous flap in that case is gold standard because of its dependability and applicability. Latissimus dorsi provides reconstruction of extensive defects, tissue with a rich blood supply and consequently better resistance to infection, and also provides a reliable and lengthy vascular pedicle giving more freedom to design the flap for optimal contour according to the size and shape of the defect. Such as Ninkovic et al.,19 we transplanted it as a functional unit, being an appropriate dynamic structure to meet the functional needs of abdominal wall reconstruction. Also, as suggested by Ninkovic,19 the split-thickness skin grafting was not excised as has been previously recommended. Deep dermabrasion was performed removing only the epithelial layer and leaving the dermis intact. The dermal layer, used as a fascia-like substitute, has adequate strength to prevent hernia formation and to restore structural integrity. This is a nearly ideal way to avoid the use of synthetic mesh and its attendant complications.

In conclusion, after final reconstruction of full-thickness abdominal wall defects using an innervated latissimus dorsi muscle free flap, the continuity, stability, and strength of the abdominal wall was obtained with the use of autogenous tissue and without the need for alloplastic material.

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Takotsubo syndrome, also known as broken heart syndrome, stress-induced cardiomyopathy, or transient left ventricle apical ballooning, is becoming an increasingly recognized cause of cardiac dysfunction in the United States. Early reports of this syndrome were primarily confined to Japan (the name of the disorder comes from tako-tsubo, meaning octopus trap); however, many cases have now been reported outside of Asia. The condition is mainly seen in postmenopausal women, involves transient apical ballooning of the myocardium, follows a physiologically stressful event, and usually resolves with conservative management. The triggers described in this syndrome have variably been acute medical illnesses, physical stressors, or emotional events. Awareness of this condition is important for trauma surgeons, emergency physicians, and cardiologists, as the impaired left ventricular function may result from the stress of a major trauma, or alternatively explain the events that led to patient injury (e.g. syncope).

CASE REPORT

A 50-year-old woman with no medical history presented to the emergency department by ambulance after a witnessed fall down a flight of stairs leading into the subway entrance. At emergency department presentation, the patient had a systolic blood pressure of 118/56 mm Hg, a heart rate of 83 bpm, respiratory rate of 18 breathes/min, and was agitated. She complained of right orbital and face pain. On physical examination, significant positive findings were a right afferent pupillary defect and swelling around the right orbit. The remainder of her physical was normal.

Her chest, cervical, and pelvic radiography studies did not disclose any abnormalities. Computed tomography of the head and face showed a right orbital wall fracture, but no intracranial abnormality. The complete blood count, serum chemistry, and coagulation studies were all normal. An electroencephalogram performed in the emergency department also did not disclose any abnormalities.

The initial diagnostic workup of the patient included an electrocardiogram (EKG), but no evaluation of cardiac enzymes. This evaluation began once the patient arrived in the surgical intensive care unit.

The first set of cardiac enzymes showed elevated values, with a troponin of 3.47 µg/L, creatine kinase of 3395 U/L, and creatine kinase isoenzyme MB of 34 ng/mL. The first EKG showed sinus rhythm and borderline 1 mm ST elevation in lead II and V2-4 (Fig. 1).

The patient was placed on telemetry monitoring and started on a β-blocker and an angiotensin converting enzyme inhibitor. The decision was made not to initiate antiplatelet and anticoagulation therapy in view of her orbital trauma. The first two-dimensional echocardiogram showed a normal left ventricle size with akinesis of the mid and distal left ventricle walls including the apex (Fig. 2). Systolic function was preserved in the basal part, with an estimated ejection fraction of 25% to 30%. A presumed diagnosis of non-ST segment elevation myocardial infarction was made, and coronary angiography was initially planned. On the third day of admission, however, the patient had a repeat echocardiogram that showed normal contractility of the entire left ventricle, suggesting a diagnosis of Takotsubo syndrome. Her ejection fraction was estimated to be 55% to 60% (Fig. 3). An EKG on the same day showed sinus bradycardia, biphasic T-waves in V2-V4, and new deep S waves in V3-V5 (Fig. 4).

In the setting of her normalized echocardiogram, the decision was made to change to a noninvasive evaluation of coronary artery disease. The patient had a dobutamine stress echocardiogram on the 12th day of hospitalization. At peak heart rate, the patient remained asymptomatic and there were no significant ST-T wave changes noted. Echocardiographic images revealed normal resting wall motion and contractility with appropriate stress-induced augmentation of regional contractility. β-Blockers were stopped at this point.

The remainder of the patient’s hospital stay was uneventful. The patient reported no adverse events when contacted 1 month after discharge.
DISCUSSION

Cases of Takotsubo syndrome have been described outside of Japan since 2003.4,5 Growing recognition has lead to an increased number of reports in the United States, but to the best of our knowledge, this is the first in the setting of blunt trauma. Although transient dilated cardiomyopathy is a relatively rare cause of cardiac dysfunction, the case emphasizes the importance of a thorough investigation of cardiovascular causes of syncope. Arrhythmia and myocardial ischemia are estimated to account for 18% of syncopal events that are seen at the hospital, but they disproportionately contribute to morbidity and mortality in...
syncopal patients. This patient had a benign hospital course with reversal of her cardiac dysfunction; however, in patients with myocardial ischemia or arrhythmia as a cause of syncope, early recognition is essential to proper management.

Classically, stress-induced cardiomyopathy is seen in postmenopausal women who present with acute chest pain after some physically or emotionally stressful event. Usually the clinical presentation and EKG findings are out of proportion to the elevation in cardiac enzymes. There are four

Fig. 3. Follow-up echocardiogram during diastole (left image) and systole (right image). There is no left ventricular regional wall motion abnormalities noted. Left ventricular systolic function appears normal. The left ventricular ejection fraction is visually estimated at 55% to 60%.

Fig. 4. Follow-up EKG. Sinus bradycardia with biphasic T-waves in V2-V4, and new deep S waves in V3-V5.
diagnostic criteria that have been proposed: transient akinesis or dyskinesis of the apical and midventricular segments, the absence of obstructive epicardial coronary disease, new ST segment elevation or T-wave inversion on EKG, and absence of significant head trauma, intracranial bleed, pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy.\(^1,7\)

The mechanism of the transient apical wall ballooning observed in this syndrome is incompletely understood. It was originally thought that myocarditis was responsible, but this is not supported by histopathologic investigations\(^8\) or gadolinium-enhanced magnetic resonance imaging findings.\(^9\)

Myocardial stunning, in the setting of microvascular ischemia has also been proposed,\(^10\) although this too is not entirely supported by Doppler flow-wire measurements.\(^11\) Excessive sympathetic stimulation is a promising explanation for apical wall ballooning, as myocardial stunning has been recognized in the setting of other intense physiologic stressors. A recent case was reported after cocaine intoxication, providing further suggestion that this may underlie the syndrome.\(^12\)

There are inconsistencies with even this hypothesis, however, and it is clear that more work is needed to better understand the pathophysiology of this syndrome.

Management of stress-induced cardiomyopathy is generally supportive. In patients that present with hypotension, emergent echocardiography is crucial to determine whether there is left ventricular outflow obstruction. These patients should receive fluid resuscitation rather than inotropic support, as the latter can worsen their outflow obstruction.

Although most case reports of Takotsubo syndrome have used angiography to evaluate coronary artery disease, our patient’s unique circumstances lead us to initially proceed with a noninvasive cardiac evaluation. In the setting of a normal dobutamine stress echocardiogram, and a normalized ejection fraction, we did not feel compelled to proceed with cardiac catheterization.

The reader should be aware that Takotsubo syndrome may be present with coexisting coronary artery disease. The trauma patient with EKG changes, wall motion abnormalities, or serum markers of myocardial ischemia should always be evaluated using American College of Cardiology/American Heart Association (ACC/AHA) guidelines.\(^13\) Accordingly, the use of \(\beta\)-blockers, angiotensin converting enzyme inhibitors, and antiplatelet agents is tailored based on risk factors and underlying cardiovascular disease.

This case introduces a new cause of cardiac dysfunction in the trauma patient; moreover, it highlights the importance of a cardiac evaluation of all trauma patients with possible syncope. Increased awareness of this rare syndrome should result in better recognition, more reporting, and an improved understanding of its cause and management.

REFERENCES

Neurogenic Pulmonary Edema Caused by a Medulla Oblongata Lesion After Head Trauma

Takeshi Matsuyama, MD, Kazuo Okuchi, MD, Takashi Nishiguchi, MD, Tadahiko Seki, MD, and Yoshinori Murao, MD

Neurogenic pulmonary edema (NPE) is characterized clinically by rapid development of pulmonary edema after cerebral damage. This abnormality consists of marked pulmonary vascular congestion, hemorrhage, and parenchymal edema. NPE typically occurs in patients with head injury, brain stem tumor, seizures, intracerebral hemorrhage, subarachnoid hemorrhage, cervical spinal cord injury, or vertebral artery occlusion. Particularly in head injuries, NPE is always associated with hypothalamic injuries because of increased intracranial pressure and the catecholamine surge is evoked by intracranial stress. These head injuries typically result in severe and fatal lesions.

Recently, experimental and clinical studies have indicated that involvement of the medulla oblongata might be the pathogenesis of NPE. We report herein a case of NPE in a patient with a medulla oblongata lesion after minor head injury.

CASE REPORT

This 33-year-old man was stricken on the neck and occiput by a piece of falling wood (about 20 kg) during manual labor. He did not lose consciousness at the time of injury. Because he complained of mild headache and sensory disturbance at the perioral region and on right forearms, he visited a nearby hospital. In the outpatient department, his consciousness was clear. Pupils were isocoric and reacted normally to light. No motor weakness was noted. Hypoesthesia was noted on the left perioral area and paresthesia on the right forearm. His blood pressure was 230/115 mm Hg and heart rate was 124 beats/min. Skull radiography revealed no fracture and head computed tomography (CT) revealed no intracranial lesions such as contusion or hemorrhage. Twenty minutes after admission, the patient complained of chest tightness and dyspnea. Trauma was not apparent on the thoracic surface. Chest radiography revealed marked diffuse edema of the lung and no costal fracture (Fig. 1). Respiration was rapid and shallow, suggesting acute respiratory distress syndrome. Body temperature was 36.3°C. He was hypotensive (76/38 mm Hg) and blood pressure was elevated by continuous infusion of dopamine. Arterial blood gas analysis revealed PaO₂ of 47.2 mm Hg and PaCO₂ of 55.2 mm Hg while breathing room air. Blood pH was 7.256 and base excess was −4.2. Endotracheal intubation was performed and high concentration oxygen was supplied. The patient was then transferred to our department for further treatment of acute respiratory distress. At admission, he was sedated and continuous artificial ventilation was initiated. Head CT was performed again but revealed no abnormalities, such as intracranial lesions. No trauma was observed on his chest or back. Chest CT revealed diffuse high-density areas around both hila, but no chest trauma such as contusion or hemothorax. The electrocardiogram and cardiac enzyme were normal, suggesting no evidence of acute cardiac failure. Magnetic resonance imaging (MRI) was performed immediately after admission. No abnormal findings were recognized in T1- and T2-weighted images. However, a hyperintense area in the left half of the medulla oblongata was recognized in diffusion image (Fig. 2). No lesions in the hypothalamic area or mass lesions inducing increased intracranial pressure were recognized. Respiration was controlled with positive end-expiratory pressure (10 mm Hg) under sedation for 2 days. Steroid pulse therapy was initiated with 1,000 mg of methylprednisolone every 2 days.

Intrathoracic blood volume index (ITBVI) and extravascular lung water index (EVLWI) were measured using a single thermodilution technique to detect the mechanisms of pulmonary edema. This investigation revealed that the ITBVI was 713 mL/m² at admission, 800 mL/m² one day after admission, and 940 mL/m² two days after admission, all within normal range (850–1000 mL/m²). EVLWI at admission was 17 mL/kg, suggesting a marked increase. One and two days after admission, EVLWI was 11 mL/kg and 10 mL/kg, within normal range (3.0–10.0 mL/kg). This suggested that cardiac preload was normal and pulmonary arte-
rial permeability increased. Pulmonary edema was primarily attributable to increased permeability of pulmonary artery alone, rather than translocation of blood from the systemic to the pulmonary circulation.

Serum concentrations of adrenalin and noradrenalin were measured at admission, and 1 and 2 days after admission. At admission, concentration of adrenalin was 0.212 ng/mL (normal: <0.12 ng/mL) and noradrenalin was 0.658 ng/mL (normal: <0.05–0.40 ng/mL). One day after admission, concentration of adrenalin was 0.047 ng/mL and noradrenalin was 0.397 ng/mL. Two days after admission, concentrations of adrenalin and noradrenalin were 0.347 ng/mL and 0.614 ng/mL, respectively. The results revealed that concentrations of serum adrenalin were highly elevated at admission and 2 days after admission, and concentrations of serum noradrenalin were moderately elevated for 3 days. Based on this study, sympathetic discharge was recognized but was not high when pulmonary edema was present.

Three days after admission, pulmonary findings improved markedly and the patient was extubated. His consciousness was clear. No motor weakness was noted. However, he complained of dysphonia and swallowing disturbance, suggesting dysfunction of the lower cranial nerves such as the glossopharyngeal or vagal nerves, corresponding to a lesion of the medulla oblongata. Seven days after admission, brain stem signs completely resolved. The medulla oblongata lesion disappeared in diffusion image of MRI, suggesting that the medullary lesion caused by head injury resulted in pulmonary edema.

DISCUSSION

NPE associated with head injury was reported in 17 soldiers after gunshot wounds in the 1960s.15 Abnormal pulmonary findings were remarkably noted in these patients, who died within 24 hours after injury. NPE is a frequent occurrence in patients with fatal head injury. Increased intracranial pressure (ICP) after head injury may contribute to the occurrence of NPE.2,16 Rapid elevation of ICP stimulates the hypothalamus or subthalamic nucleus directly or indirectly, resulting in increased sympathetic activity and marked elevation of serum catecholamine levels. The generally accepted cause is as follows. Massive sympathetic discharge produces severe systemic and pulmonary hypertension and increased venous return. Blood is translocated from the systemic to the pulmonary circuit by remaining systemic vasoconstriction and pulmonary blood volume markedly increases.

Several clinical and experimental studies have indicated that brain stem lesions are involved in the pathogenesis of NPE.13,14,17–19 NPE was recognized in a patient with brain stem hemorrhage of a series of patients with cerebral hemorrhage of various locations.8 In a series of bulbar poliomyelitis, a patient with pathologic changes in the region of the dorsal motor nucleus of the vagus and medial reticular nuclei of the medulla developed NPE.20 Several cases of NPE associated with brain stem tumor have been reported.5,6,21,22 Brown reported NPE was caused by postoperative posterior medullary edema in a patient with dorsal medullary syrinx, and speculated that the edema in regions of the nucleus tractus solitarii and dorsal motor nucleus of the vagus contribute to the pathogenesis of NPE.5 Ochiai reported an association between NPE and ruptured vertebral artery aneurysm.21 Deformation of the medulla oblongata because of subarachnoid hemorrhage contributes to the occurrence of NPE.

Interconnections between the nucleus tractus solitarii, hypothalamus, and A-1 region in the medulla have been identified in an experimental study.23 The destruction of this interconnection disturbed respiratory control. The solitary nucleus in the dorsal medulla functions as a suppressor of sympathetic activity,24 and the A-1 adrenergic region at the ventrolateral site of the medulla oblongata stimulates the solitary nucleus.13 The solitary nucleus in the dorsal medulla may be an important site of integration for central nervous system control of cardiopulmonary function. Stimulation of the solitary nucleus produces hypotension and bradycardia, suggesting that the solitary nucleus inhibits sympathetic cardiac tone.23 Destruction of the ventrolateral medulla oblongata including the solitary nucleus causes a catecholamine
surge and sympathetic vasoconstriction. Darragh and Simons reported that bilateral solitary nucleus lesions resulted in a marked rise in pulmonary arterial pressure without changes in systemic or left atrial pressure. This indicates that specific lesions of the solitary nucleus may alter pulmonary vascular pressure and transcapillary fluid leak independent of effects on the systemic circulation. This may be considered a neural-mediated effect. This hypothesis was supported by our investigation, which demonstrated that intrathoracic blood volume index was normal and extravascular lung volume was initially elevated but decreased after treatment.

In our case, at admission the patient showed hypertension and tachycardia, which may be caused by a catecholamine surge. However, after admission, he became hypotensive despite a consistent catecholamine surge. This may have been caused by circulatory suppression because of acute respiratory distress syndrome. Transient medulla oblongata lesions after occipital impact may have contributed to the rapid development of NPE. Besides hypothalamic theory, a lesion of the medulla oblongata alone can cause NPE in another fashion.

REFERENCES


Hyperglycemia is a common event in the Intensive Care Unit (ICU) for a variety of reasons and its impact on management and outcome has been increasingly investigated. Tight glucose control has been associated with decreased ICU mortality in selected patient populations. The applicability of these findings to different subsets of critically ill patients continues to be debated as do the target goals of glycemic control that appropriately balance therapeutic benefit with the potential adverse consequences of hypoglycemia. Nevertheless, several groups such as the Joint Commission on Accreditation of Healthcare Organizations and the Volunteer Hospital Association have proposed that tight glycemic control be incorporated into routine care practices and assessed as an index of the quality of ICU care. It is likely that this topic will remain an area of interest and active debate until the role of hyperglycemia and glucose control in the critically ill patient is better understood. The results of ongoing large randomized controlled trials should become available in the years ahead and are likely to increase our understanding in this area.

As part of the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program, the participating investigators reviewed the available evidence and developed a standard operating procedure (SOP) for the administration of insulin and the management of plasma glucose levels in the critically ill trauma patient. It bears mentioning that none of the major trials published to date contain substantial populations of injured patients, and so the efficacy of tight glycemic control in trauma patients has not been prospectively evaluated. Hyperglycemia in injured patients, however, has been correlated with adverse outcome. The primary purpose of this SOP was to rationally apply the currently available data to injured patients and to standardize care for the injured patients enrolled through the program. No attempt was made to grade the available evidence but rather to develop a unified approach to the management of the injured patient in the context of the available published information.

Protocol Goals
- Provide guidelines for the management of glucose control in critically ill trauma patients.
- Minimize the incidence of hypoglycemia associated with serum glucose control management.

Protocol Rationale

Rationale for Strict Glycemic Control in Trauma Patients

Hyperglycemia and relative insulin resistance are established metabolic consequences of shock and trauma in critically ill patients. Hyperglycemia can contribute to toxic cellular effects that can promote systemic inflammation and cellular dysfunction. The adverse consequences of hyperglycemia on organ function have been recently reviewed. Many of the adverse cellular and tissue effects of hyperglycemia have been established in vitro or in well-controlled animal models, and their direct relevance to critically ill patients is hypothetical. Nevertheless, hyperglycemia has been associated with increased hospital mortality in several large retrospective studies of heterogeneous populations of critically ill adults. In trauma patients, admission hyperglycemia has also been associated with poor outcome. What
has not been clearly defined by studies of injured patients as whether admission hyperglycemia is a reflection of the magnitude of the physiologic response to the initial injury or a contributor to mortality because of the specific deleterious effects of elevated circulating glucose levels.

The impact of a policy of strict glucose control on outcome of critically ill trauma patients has not been specifically tested. Randomized trials of strict glycemic control in other groups of critically ill patients are available for analysis but these studies include small numbers of injured patients. The most widely cited trial involved 1,548 surgical ICU patients prospectively randomized to intensive insulin therapy (goal glucose of 80–110 mg/dL) or conventional therapy (goal glucose of 180–200 mg/dL) by Van den Berghe et al.\textsuperscript{11} Intensive insulin therapy was associated with a reduction in overall mortality from 8.0% in the conventional group to 4.6% in the treatment group ($p < 0.04$) with the effect on the mortality rate more pronounced in the patients that required ICU care for >5 days. The authors concluded that the mortality benefit was primarily a result of a reduction in sepsis-related multiple organ failure. In this study, more than 60% of enrolled patients underwent cardiac surgery and only approximately 5% of enrolled patients were trauma patients. Hypoglycemia, defined as a blood glucose level <40 mg/dL, occurred more frequently in the treatment group (5.1%) than in the control group (0.7%), although no major consequences of hypoglycemia were reported. In these patients, the median ICU length of stay (LOS) was 3 days, the median duration of mechanical ventilatory support was 2 days, and all patients were started on an aggressive regimen of total parenteral nutrition or combined total parenteral nutrition and enteral nutrition on day 1. Additional data on the nutritional support provided to these patients and the association between insulin administration and complications were provided in a subsequent report by these authors on the same group of patients.\textsuperscript{12} Although any beneficial effects of a policy of strict glycemic control might be a result of (1) maintenance of euglycemia or (2) pharmacologic effects of exogenous insulin administration, the authors concluded that it was the former that was most closely associated with the observed beneficial effects.

A prospective randomized study on the effect of glucose control and insulin administration was published by Finney et al.\textsuperscript{13} They studied 531 critically ill adults and found that increased insulin administration was significantly associated with risk of death regardless of the level of serum glucose or the presence of diabetes.\textsuperscript{13} They concluded that glucose control, as opposed to insulin dose or administration per se, contributed to ICU mortality. No target glucose range was mandated in this study, although a target range of 90 mg/dL to 145 mg/dL was sought. Approximately 85% of enrolled patients were cardiac surgery patients, approximately 12% were medical patients, and there were no general surgery or trauma patients enrolled in this study.

A study on strict glycemic control in medical ICU patients was published by Van den Berghe et al.\textsuperscript{14} This study was prospective and randomized and evaluated 1,200 patients with a variety of nonsurgical diagnoses on an intention-to-treat basis. As in the earlier study from this group, conventionally treated control patients had insulin infusions started if their blood glucose exceeded 215 mg/dL with a target glucose range of 180 mg/dL to 200 mg/dL, whereas the treatment group received insulin for blood glucose levels >110 mg/dL with a target glucose range of 80 mg/dL to 110 mg/dL.\textsuperscript{14} In an unstratified analysis, patients randomized to strict glycemic control with intensive insulin therapy had a reduction in new onset renal dysfunction, earlier weaning from mechanical ventilation, and earlier ICU and hospital discharge although overall mortality was similar compared with that of the control group. For subjects requiring ≥3 days of ICU care, intensive insulin therapy was associated with reduced overall mortality as well as more rapid weaning from mechanical ventilation and earlier ICU and hospital discharge. In patients who stayed <3 days in the ICU, strict glycemic control was associated with an apparent increase in mortality compared with conventional treatment. As in the earlier study by this group, the total quantity of calories administered parenterally was high despite the investigator’s attempt to institute early enteral feeding, so excessive exogenous glucose administration was not completely eliminated as a confounding variable.\textsuperscript{14} Approximately 65% of the patients in this study had a length of ICU stay in excess of 3 days although the mean and median ICU lengths of stay were not reported. This group has also demonstrated decreased total hospital costs in patients previously enrolled in studies of intensive insulin therapy compared with those of control subjects.\textsuperscript{15}

Other beneficial effects of strict glycemic control have been proposed based on subgroup analyses of subjects enrolled in these prospective trials. Hepatic mitochondrial ultrastructure and function were better in biopsy samples taken from subjects undergoing strict glycemic control compared with those taken from conventionally treated subjects, although similar findings were not present in skeletal muscle.\textsuperscript{16} Intensive insulin therapy in this group of patients is also associated with decreased serum triglycerides, increased serum high-density lipoproteins, and increased skeletal muscle glucose transporter messenger RNA levels.\textsuperscript{17}

It has been suggested that the quantity of glucose infused via intravenous (i.v.) fluids, presumably as an index of the magnitude of hyperglycemia, can significantly contribute to ICU mortality.\textsuperscript{4} A retrospective analysis of 273 critically ill patients with an ICU LOS >7 days found that Acute Physiology and Chronic Health Evaluation II score and the mean daily amount of glucose infused were the only independent predictors of mortality in a multivariate logistic regression analysis.\textsuperscript{4} These patients, on average, received relatively low (mean, 66 g glucose/d) quantities of infused glucose. A protocol for strict glycemic control was not used in this population of patients because they were hospitalized before 2002 and glucose measurements were performed relatively infre-
Rationale for the Use of Insulin to Achieve Tight Glycemic Control

The technique of blood glucose measurement may significantly impact the level of blood glucose obtained and therefore affect clinical treatment decisions in critically ill adults. Bedside testing with metered analysis of capillary blood, metered analysis of arterial blood, and blood gas/chemistry analysis of arterial blood all had significant variability compared with central chemistry laboratory measurement. It has not been directly tested, however, whether different methods of glucose measurement significantly influence the ability to achieve tight glycemic control or affect overall patient outcome. This study does suggest that improvement in the accuracy of bedside testing will need to continue as aggressive insulin therapy protocols are enacted to avoid the morbidity associated with clinically significant hypoglycemia.

The method of insulin administration has also been studied. Administration of i.v. insulin using a protocol has been shown to be more effective at lowering blood glucose than intermittent subcutaneous (s.c.) insulin administration driven by individual physician preference. This study has been used to support the hypothesis that i.v. insulin is more efficacious than s.c. insulin. It is not clear, however, if the reported benefit in this study was a result of the protocolized insulin administration compared with nonprotocolized administration or if the route of delivery (i.v. vs. s.c.) was important. A trial comparing i.v. insulin administration to intermittent s.c. insulin administration in critically ill adults has not yet been performed.

As discussed above, much of the work on intensive insulin therapy has been performed in nontrauma cardiac surgery patients or in medical ICU patients. The applicability of these studies to broad-based general surgical ICUs, neurosurgical ICUs, or trauma ICUs remains unproven. Additionally, debate has been stimulated by the relatively high mortality rate in the conventionally treated control group in the studies by Van den Berghe, raising the question of whether the benefit seen in published studies is a lowering of the mortality rate with intensive insulin therapy or an artificial increase in mortality rate in the control group, potentially because of liberal use of early parenteral nutrition and hypertonic glucose infusions. Some authors have suggested that the benefit of insulin therapy and strict glycemic control may vary considerably depending on the case mix of the respective ICU. The risk-benefit ratio may therefore vary across institutions and critical care units. Reports from surgical ICUs have shown that lowering of blood glucose can be readily achieved with an insulin infusion protocol with a low incidence (1%–3.5%) of hypoglycemia. This study evaluated protocol compliance, however, and no attempt was made to evaluate effects on patient outcome.

In trauma patients, an interventional trial has not yet been prospectively performed but several retrospective studies are available for analysis. Laird et al. performed a retrospective analysis of 516 trauma patients correlating early hyperglycemia (day 1 or 2 in the ICU) to outcome and stratified glucose levels as ≥110 mg/dL, ≥150 mg/dL, and ≥200 mg/dL. They performed multivariate logistic regression to determine independent predictors of mortality and found that glucose ≥200 mg/dL but not ≥150 mg/dL or ≥110 mg/dL independently correlated with mortality. They suggested that the effect of glucose control on mortality may vary depending on the patient population and suggested that target glucose levels may be different for different ICU populations. In this study, however, they did not evaluate glucose levels beyond day 2 of hospitalization and the lack of specific intervention in this retrospective study makes drawing firm conclusions difficult.

In trauma patients, the optimal guideline for the regulation of serum glucose levels, the best method of proper glucose monitoring, or the most efficacious manner to treat high glucose levels has not been adequately studied. Given the acknowledged limitations of the published studies (high glucose infusions, higher than expected mortality in control groups, low ICU LOS, predominance of cardiac surgery patients) and the inherent difficulties in managing patients with multiple injuries who may have ongoing fluid resuscitation, multiple trips to the operating room interrupting enteral nutrition, and the presence of brain injuries in which the deleterious effects of hypoglycemia may be more pronounced, the participating investigators were charged with balancing existing data with an acceptable margin of safety. Infusions of i.v. insulin and tight control of blood glucose levels also require considerable nursing resources. Until large randomized prospective trials that are currently underway are published or additional trauma-specific studies are performed, the optimal target glucose level and the best method for insulin administration in trauma patients will be difficult to assess with certainty. The reader should understand that this is an area of intense clinical investigation and new studies on glucose control in critically ill patients are being published regularly. Emerging data may identify subsets of patients with a different risk-benefit ratio or those who may benefit from different target glucose levels.

Based on the available evidence, the Inflammation and Host Response Investigators acknowledge that there is no level 1 data to directly support the clinical goal of tight glycemic control in severely injured patients. However, given the association between hyperglycemia and increased mortality in injured patients, as well as the benefit seen in some groups of critically ill patients, controlling hyperglycemia seems to be a prudent component of ICU care as long as episodes of hypoglycemia can be avoided. The investigators reached consensus to adopt the strategies that have been successful in other critically ill populations and have devel-
Protocol Summary

A. All ICUs should have a guideline in place for the measurement and control of blood glucose in critically ill trauma patients. The intensity of the monitoring protocol may vary according to local medical practice, nutritional practice, frequency of operative intervention, and frequency of hyperglycemia as determined by unit quality improvement processes. A minimum frequency of blood glucose measurement every 4 to 6 hours should be performed for critically ill patients whose glucose levels fall within the target range. More frequent measurement of glucose (every 1–2 hours) is recommended initially for patients whose glucose levels are out of the target range, who are receiving glucose infusions, and for patients whose glucose level is difficult to control.

B. Glucose levels should be measured by point-of-care bedside devices. Samples of arterial whole blood drawn through an existing arterial line are preferred. If an arterial line is not available, venous whole blood drawn through a central venous catheter remote from concentrated glucose infusions may be used. Theoretical concerns regarding the accuracy of capillary glucose measurements (“fingersticks”) in critically ill ICU patients have not been thoroughly tested. Calibration and proper function of the measuring devices should be assessed routinely according to manufacturer’s instructions.

C. Monitoring and control of blood glucose should begin once resuscitation is complete and the patient is stable in the ICU. It is not known if resuscitation-induced peripheral edema, local or systemic hyperperfusion, altered bioavailability, and increased volume of distribution of trauma patients can interfere with dosing and absorption of s.c. injections, and so i.v. insulin administration is preferred.

D. Careful attention to avoidance of hypoglycemia must be provided. Glucose monitoring and insulin administration should be adjusted and the frequency of glucose measurements increased if enteral nutrition, parenteral nutrition, or glucose-containing fluids are either increased or decreased.

E. Insulin is metabolized and excreted by the liver and kidney. Critically ill patients with hepatic or renal failure may need more frequent glucose measurements and should have exogenous insulin administered carefully.

Protocol Details

1. Exogenous insulin administration should be considered for critically ill patients with persistent blood glucose levels >110 mg/dL.

2. Blood glucose levels should initially be measured a minimum of every 2 to 4 hours. If levels are persistently elevated, insulin should be administered by i.v. push and an insulin infusion should begin. A sample adjusted initiation schedule is provided in Table 1.

3. Adjustment of the insulin infusion should be performed every 1 to 2 hours while an insulin infusion is continuing. Insulin administration should be titrated to blood glucose levels using a combination of i.v. bolus insulin and adjustment of the insulin continuous infusion. A schedule of adjustments is provided in Tables 2 and 3.

4. If enteral nutrition, parenteral nutrition, or glucose-containing i.v. fluids are stopped, the insulin infusion should be decreased by 50% and blood glucose rechecked in 1 hour.

5. If the blood glucose decreases by ≥50 mg/dL and remains elevated, the infusion should be maintained at its current rate and the blood glucose rechecked in 1 hour.

6. If the insulin infusion reaches 30 U/h, notify the treating physician. Glucose measurements should be checked every hour and additional insulin administered as bolus i.v. doses as outlined in Table 2 but the continuous infusion should not be increased. If the insulin infusion remains at 30 U/h and glucose remains difficult to control, reevaluate for treatable causes (i.e. excessive glucose infusion, exogenous steroid administration). Consider consultation with an endocrinologist.

7. For patients with a serum creatinine ≥2.0 mg/dL, adjust the insulin infusion but avoid bolus insulin administration. Consider increasing the frequency of glucose measurements to hourly until a steady state is reached.

8. Consider hourly glucose measurements for patients whose glucose is difficult to control or at the discretion of the bedside physician or nurse.

9. Intensive glycemic control should be discontinued upon transfer from the ICU. Institutions should be encouraged to develop guidelines for glucose control during the transition from intensive care to full recovery. An appropriate schedule of glucose measurements, range of acceptable

### Table 1 Initiation of Insulin Administration

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dL)</th>
<th>Bolus i.v. Push (U)</th>
<th>Infusion Rate (U/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>111–150</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>151–200</td>
<td>2</td>
<td>2</td>
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<tr>
<td>201–250</td>
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<td>4</td>
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<tr>
<td>301–350</td>
<td>8</td>
<td>4</td>
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<tr>
<td>&gt;350</td>
<td>10</td>
<td>4</td>
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</table>

Indications are critically ill patients with persistent blood glucose >110 mg/dL.

Monitoring: check blood glucose q 2 h and q 1 h prn. If tube feeds, TPN or fluids with D5W are stopped; decrease insulin infusion rate by 50% and check blood glucose q 1 h. If blood glucose decreases by >50 mg/dL and is still elevated; keep infusion at current rate and recheck blood glucose in 1 h: do not give bolus for serum creatinine (Scr) ≥2 mg/dL.
Table 2 Adjustments of Insulin Infusion

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dL)</th>
<th>Bolus i.v. Push (U)</th>
<th>Infusion Rate (U/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>0</td>
<td>D/c infusion; give ampule D50 i.v. push; recheck blood glucose in 30 min AND if blood glucose &gt;80, resume insulin infusion at 50% of previous rate</td>
</tr>
<tr>
<td>60–79</td>
<td>0</td>
<td>D/c infusion; recheck blood glucose in 30 min and if blood glucose &gt;80, resume insulin infusion at 50% of previous rate</td>
</tr>
<tr>
<td>80–110</td>
<td>0</td>
<td>No change; if blood glucose continues to decrease within desired range over 4 h; decrease rate by 20%*</td>
</tr>
<tr>
<td>111–150</td>
<td>0</td>
<td>Increase rate by 20%*</td>
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<tr>
<td>151–200</td>
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<td>Increase rate by 20%*</td>
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<td>201–250</td>
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<td>Increase rate by 20%*</td>
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<td>&gt;350</td>
<td>10</td>
<td>Increase rate by 20%*</td>
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</table>

* See Table 3 for rounded 20% adjustments (increase or decrease).

Table 3 Twenty Percent Adjustments per Rate of Infusion

<table>
<thead>
<tr>
<th>Current Rate (U/h)</th>
<th>Increase Rate (20%)</th>
<th>Decrease Rate (20%)</th>
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<tbody>
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<td>0.5</td>
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VI. Blood Glucose Control in Trauma Patients

glucose levels, and schedule of insulin administration should be based on the patient’s pre-existing medical problems, presence or absence of diabetes, nutritional regimen, and institutional resources.

Summary

Strict glycemic control may offer significant benefit in the care of the critically ill trauma patient. Randomized, prospective controlled trials on the effects of strict glycemic control in injured patients have not yet been performed. The potential problems with currently available trials, associated with the potential ramifications of hypoglycemia in subsets of trauma patients, require caution in adopting an extremely aggressive approach to glucose control. However, improved glucose control appears to be a promising and prudent approach to decreasing morbidity in injured patients. The goal of this SOP was to standardize the management of injured patients enrolled in the Inflammation and Host Response to Injury Large-Scale Collaborative Program across multiple clinical sites. It is based on the available medical evidence and expert opinion when evidence is not available. The steps in this SOP represent one method of attempting to reach the goal of improved glucose control in injured patients and the authors acknowledge that other methods may exist that may be equally effective. Additional prospective randomized controlled trials will likely provide additional information that may stimulate further revisions of this SOP as the role of glucose management in critically ill trauma patients is better defined.
ACKNOWLEDGMENTS

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REFERENCES

Practice Management Guidelines for the Screening of Thoracolumbar Spine Fracture

Jose J. Diaz, Jr., MD, Daniel C. Cullinane, MD, Daniel T. Altman, MD, Faran Bokhari, MD, Joseph S. Cheng, MD, John Como, MD, Oliver Gunter, MD, Michele Holevar, MD, Rebecca Jerome, MS, Stanley J. Kurek, Jr., DO, Manuel Lorenzo, MD, Vicente Mejia, MD, Maurizio Miglietta, MD, Patrick J. O’Neill, PhD, MD, Peter Rhee, CAPT, MD, Ronald Sing, MD, Erik Streib, MD, and Steven Vaslef, MD, for the EAST Practice Management Guideline Committee

Background: Fractures to the thoracolumbar spine (TLS) commonly occur because of major trauma mechanisms. In one series, 4.4% of all patients arriving at a Level I trauma center were diagnosed as having TLS fracture. Approximately 19% to 50% of these fractures in the TLS region will be associated with neurologic damage to the spinal cord. To date there are no randomized studies and only a few prospective studies specifically addressing the subject. The Eastern Association for the Surgery of Trauma organization Practice Management Guidelines committee set out to develop an EBM guideline for the diagnosis of TLS fractures.

Methods: A computerized search of the National Library of Medicine and the National Institutes of Health MEDLINE database was undertaken using the PubMed Entrez (www.pubmed.gov) interface. The primary search strategy was developed to retrieve English language articles focusing on diagnostic examination of potential TLS injury published between 1995 and March 2005. Articles were screened based on the following questions. (1) Does a patient who is awake, nonintoxicated, without distracting injuries require radiographic workup or a clinical examination only? (2) Does a patient with a distracting injury, altered mental status, or pain require radiographic examination? (3) Does the obtunded patient require radiographic examination?

Results: Sixty-nine articles were identified after the initial screening process, all of which dealt with blunt injury to the TLS, along with clinical, radiographic, fluoroscopic, and magnetic resonance imaging evaluation. From this group, 32 articles were selected. The reviewers identified 27 articles that dealt with the initial evaluation of TLS injury after trauma.

Conclusion: Computed tomography (CT) scan imaging of the bony spine has advanced with helical and currently multidetector images to allow reformatted axial collimation of images into two-dimensional and three-dimensional images. As a result, bony injuries to the TLS are commonly being identified. Most blunt trauma patients require CT to screen for other injuries. This has allowed the single admitting series of CT scans to also include screening for bony spine injuries. However, all of the publications fail to clearly define the criteria used to decide who gets radiographs or CT scans. No study has carefully conducted long-term follow-up on all of their trauma patients to identify all cases of TLS injury missed in the acute setting.

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by those caring for acutely injured patients. Radiographic screening of the spinal axis can be performed by a number of means. Plain radiography, computed tomography (CT), and magnetic resonance imaging (MRI) all have roles in the screening and evaluation of acute traumatic injuries to the TLS. Although there are numerous clinical studies addressing screening of the TLS, to date there are no randomized studies and only a few prospective studies specifically addressing the subject. Several questions are of particular concern for medical, economic, and legal reasons.

**PROCESS**

**Identification of References**


Titles and abstracts were reviewed to determine relevance and identify articles, which included primary data, with consultation of the full-text article when the citation or abstract data were inadequate. To supplement this search strategy, the PubMed “Related Articles” feature was used to review the first 100 related citations for each of the selected articles retrieved by the primary strategy. Sixty-nine articles were identified after the initial screening process, all of which dealt with blunt injury to the TLS, along with clinical, radiographic, fluoroscopic, and MRI evaluation. These set of articles were screened based on the following questions being asked by the proposed Practice Managed Guideline:

1. Does a patient who is awake, nonintoxicated, and without distracting injuries require radiographic workup or a clinical examination only?
2. Does a patient with a distracting injury, altered mental status, or pain require radiographic examination?
3. Does the obtunded patient require radiographic examination?

From this group, 32 articles where selected, and an evidentiary table was constructed (Table 1). The reviewers identified 27 articles that dealt with the initial evaluation of TLS injury after trauma. These articles were used to create the recommendations (Fig. 1 describes the methodology).

**Quality of the References**

The Eastern Association for the Surgery of Trauma (EAST)”s Utilizing Evidence Based Outcome Measures to Develop Practice Management Guidelines: A Primer, was utilized as a quality assessment instrument applied to the development of this protocol.

The workgroup for the Practice Management Guidelines for the diagnosis of traumatic blunt TLS injury consisted of 15 trauma surgeons, 1 neurosurgeon, and 1 orthopedic spine surgeon.

The articles were distributed among committee members for review. Each article was reviewed by at least three reviewers. Each article was reviewed with the three previously mentioned questions in mind, and a summarized conclusion of the study was submitted. Reviewers were asked to classify each reference as class I, class II, or class III data. Articles that were not useful to the discussion were omitted from the final evidentiary table.

The quality assessment instrument applied to the references was developed by the Brain Trauma Foundation and subsequently adopted by the EAST Practice Management Guidelines Committee. Articles were classified as class I, II or III according to the following definitions:

- **Class I:** A prospective randomized clinical trial. There were no class I articles reviewed.
- **Class II:** A prospective noncomparative clinical study or a retrospective analysis based on reliable data. Thirteen class II articles were reviewed.
- **Class III:** A retrospective case series or database review. Fifty-six class III articles were reviewed.

Because of the lack of any class I references, no level I recommendations could be made regarding the questions at hand. Level II recommendations supported by class II data were thought to be reasonably justifiable by available scientific evidence and strongly supported by expert opinion. Level III recommendations were based on class III data, where adequate scientific evidence is lacking, but the recommendation is widely supported by available data and expert opinion.

**RECOMMENDATIONS**

See the flow diagram in Figure 2.

A. Does a patient who is awake without distracting injuries require radiographic workup or clinical examination?
1. **Level I:** There is insufficient evidence to support a level I recommendation for the management guideline.
### Table 1 The Evidence for Thoracolumbar Spine Radiographic Clearance

<table>
<thead>
<tr>
<th>Article No.</th>
<th>First Author</th>
<th>Year</th>
<th>Reference Details</th>
<th>Class</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Frankel et al.</td>
<td>1994</td>
<td>Indications for obtaining surveillance thoracic and lumbar spine radiographs. <em>J Trauma.</em> 1994;37: 673–676</td>
<td>II/III</td>
<td>Clinical examination alone may be inadequate for evaluation. Patients with abnormal neurologic examination, significant mechanism, pain and tenderness on examination, intoxication, and significant associated injuries require radiographic workup. Plain X-ray examinations should be obtained for spine clearance.</td>
</tr>
<tr>
<td>2</td>
<td>Gestring et al.</td>
<td>2002</td>
<td>Evaluation of the lower spine after blunt trauma using abdominal computed tomographic scanning supplemented with lateral scanograms. <em>J Trauma.</em> 2002;53:9–14</td>
<td>II</td>
<td>High definition CT scout radiographs of TL spines superior to plain radiographs in detecting fracture. Asymptomatic patients may have significant fractures and clinical examination alone is inadequate to exclude TL spine fracture, particularly if there is altered mental status, pain and tenderness, and significant mechanism.</td>
</tr>
<tr>
<td>3</td>
<td>Hauser et al.</td>
<td>2003</td>
<td>Prospective validation of computed tomographic screening of the thoracolumbar spine in trauma. <em>J Trauma.</em> 2003;55:228–235</td>
<td>II</td>
<td>CT scan is more sensitive and specific than plain radiographs for the detection of TL spine fractures. CT scan is also much faster than plain radiographs as it is usually performed at the initial trauma evaluation. Multidetector CT scan is superior to plain radiographs for detection of TL spine fractures. Three-millimeter slices may be superior to 5-mm slices for the detection of unstable fractures, but no fractures were missed with 5-mm cuts.</td>
</tr>
<tr>
<td>4</td>
<td>Herzog et al.</td>
<td>2004</td>
<td>Traumatic injuries of the pelvis and thoracic and lumbar spine: does thin-slice multidetector-row CT increase diagnostic accuracy? <em>Eur Radiol.</em> 2004;14:1751–1760</td>
<td>II</td>
<td>Patients with pain, tenderness, altered sensorium, abnormal peripheral neurologic examination, and distracting injury require at least plain radiographs. If none of the previous risk factors are present, the patient can be cleared clinically, although no confirmatory tests were performed.</td>
</tr>
<tr>
<td>5</td>
<td>Holmes et al.</td>
<td>2003</td>
<td>Prospective evaluation of criteria for obtaining thoracolumbar radiographs in trauma patients. <em>J Emerg Med.</em> 2003;24:1–7</td>
<td>II</td>
<td>MRI may be useful for following known fractures and predicting outcomes in TL spine fractures. Multiply injured patients were excluded from this study. Does not address screening.</td>
</tr>
<tr>
<td>6</td>
<td>Oner FC</td>
<td>2002</td>
<td>Some complications of common treatment schemes of thoracolumbar spine fractures can be predicted with magnetic resonance imaging: prospective study of 53 patients with 71 fractures. <em>Spine.</em> 2002;27:629–636</td>
<td>II</td>
<td>CT scan (particularly helical reformatted 2.5-mm cuts) is more sensitive and specific for detection of TL spine fracture than plain radiographs. One noted advantage was a decreased time to clearance or diagnosis. There is potentially less radiation exposure with plain radiographs than CT.</td>
</tr>
<tr>
<td>7</td>
<td>Sheridan et al.</td>
<td>2003</td>
<td>Reformatted visceral protocol helical computed tomographic scanning allows conventional radiographs of the thoracic and lumbar spine to be eliminated in the evaluation of blunt trauma patients. <em>J Trauma.</em> 2003;55: 665–669</td>
<td>II</td>
<td>Patients with altered mental status, pain, or distracting injury require radiologic workup of TL spine as clinical examination may be unreliable. Awake patients with normal mental status, neurologic, and physical examinations are able to be cleared clinically.</td>
</tr>
<tr>
<td>8</td>
<td>Terregino et al.</td>
<td>1993</td>
<td>Selective indications for thoracic and lumbar radiography in blunt trauma. <em>J Trauma.</em> 1993;35:979</td>
<td>II</td>
<td>Patients in whom a complete neurologic examination cannot be performed or is likely to be unreliable require radiologic workup of spine for clearance. Multitrow detector CT scan is superior to plain radiographs for detection and screening of TL spine fracture in trauma patients. Patients in this study underwent both conventional radiography as well as CT scanning for evaluation.</td>
</tr>
<tr>
<td>9</td>
<td>van Beek EJR</td>
<td>2000</td>
<td>Upper thoracic spinal fractures in trauma patients—a diagnostic pitfall. <em>Injury.</em> 2000;31:219–223</td>
<td>II</td>
<td>CT scan is sensitive in evaluation of spinal fracture. Mechanism of injury may be predictive of need for radiographic workup of TL spine.</td>
</tr>
<tr>
<td>10</td>
<td>Wintermark M</td>
<td>2003</td>
<td>Thoracolumbar spine fractures in patients who have sustained severe trauma: depiction with multi-detector row CT. <em>Radiology.</em> 2003;227:681–689</td>
<td>II</td>
<td>Multitrow detector CT scan is superior to plain radiographs for detection and screening of TL spine fracture in trauma patients. Patients in this study underwent both conventional radiography as well as CT scanning for evaluation.</td>
</tr>
<tr>
<td>11</td>
<td>Bensch FV</td>
<td>2004</td>
<td>Spine fractures in falling accidents: analysis of multidetector CT findings. <em>Eur Radiol.</em> 2004;14:618–624</td>
<td>III</td>
<td>Multitrow detector CT scan is superior to plain radiographs for detection and screening of TL spine fracture in trauma patients. Patients in this study underwent both conventional radiography as well as CT scanning for evaluation.</td>
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<tr>
<td>12</td>
<td>Brandt MM</td>
<td>2004</td>
<td>Computed tomographic scanning reduces cost and time of complete spine evaluation. <em>J Trauma.</em> 2004;56:1022–1026</td>
<td>III</td>
<td>CT scan is superior to plain radiographs for detection and screening of TL spine fractures. Patients underwent both conventional radiography as well as CT scan. Smaller study than Radiology 2003. Mechanism of injury may be predictive of need for radiographic workup of TL spine.</td>
</tr>
<tr>
<td>13</td>
<td>Cooper et al.1</td>
<td>1995</td>
<td>Falls and major injuries are risk factors for thoracolumbar fractures: cognitive impairment and multiple injuries impede the detection of back pain and tenderness. <em>J Trauma.</em> 1995;38:692–695</td>
<td>III</td>
<td>Patients with altered mental status or distracting injuries require radiographic screening for TL spine fracture as clinical examination may be unreliable or unavailable.</td>
</tr>
<tr>
<td>14</td>
<td>Dai LY</td>
<td>2004</td>
<td>Thoracolumbar fractures in patients with multiple injuries: diagnosis and treatment—a review of 147 cases. <em>J Trauma.</em> 2004;56:348–355</td>
<td>III</td>
<td>Patients with significant mechanism of injury should be suspected of having TL spine fracture and further workup is required, including plain radiographs, which must be read by experienced physicians.</td>
</tr>
<tr>
<td>18</td>
<td>Hsu et al.14</td>
<td>2003</td>
<td>Thoracolumbar fracture in blunt trauma patients: guidelines for diagnosis and imaging. <em>Injury.</em> 2003;34:426–433</td>
<td>III</td>
<td>Clinical examination may be inadequate to exclude TL spine injury particularly in the setting of back pain and tenderness, local examination findings consistent with fracture, decreased level of consciousness, cervical spine injury, distracting injury, and intoxication. Plain radiographs should be obtained in patients at risk; CT is superior to plain films on the basis of other studies.</td>
</tr>
<tr>
<td>21</td>
<td>Meldon and Moettus16</td>
<td>1995</td>
<td>Thoracolumbar spine fractures: clinical presentation and the effect of altered sensorium and major injury. <em>J Trauma.</em> 1995;39:1110–1114</td>
<td>III</td>
<td>Clinical examination alone is unable to exclude TL spine fracture in the setting of altered sensorium, distracting injury, neurologic deficit, or pain and tenderness on examination. Plain films should be obtained on these patients for screening.</td>
</tr>
<tr>
<td>22</td>
<td>Oner FC</td>
<td>2002</td>
<td>Classification of thoracic and lumbar spine fractures: problems of reproducibility. A study of 53 patients using CT and MRI. <em>Eur Spine J.</em> 2002;11:235–245</td>
<td>III</td>
<td>MRI may be used to classify known spine fractures. No mention is made with regard to screening patients in the acute setting.</td>
</tr>
<tr>
<td>23</td>
<td>Oner FC</td>
<td>1999</td>
<td>MRI findings of thoracolumbar spine fractures: a categorization based on MRI examinations of 100 fractures. <em>Skeletal Radiol.</em> 1999;28:433–443</td>
<td>III</td>
<td>MRI may be used to classify known spine fractures. No mention is made with regard to screening patients in the acute setting.</td>
</tr>
</tbody>
</table>
2. Level II: The articles reviewed provide evidence to support (c) level II recommendations.
   a. Trauma patients should be examined by a qualified attending physician.
      i. Those qualified include trauma surgeons, emergency physicians, or spine surgeons (orthopedic or neurosurgical).
   b. Trauma patients who are awake, without any evidence of intoxication with ethanol or drugs, with normal mental status, neurologic, and physical examinations may be cleared clinically.
   c. The mechanism of injury is an important determinant for further workup for this category of patients. If a high energy mechanism of injury is known or suspected, radiographic screening is warranted.
      i. Falls from significant height (>10 feet), motor vehicle or motorcycle or all-terrain vehicle crash with or without ejection, pedestrians struck, assault, sport or crush injury, bicycle, and a concomitant cervical spine fracture are considered to have high energy mechanism of injury.

3. Level III: There is level III evidence to further support the above mentioned level II recommendations.
   a. In general falls from significant height, motor vehicle crashes, struck pedestrians, etc. are considered to have high energy mechanism of injury.

B. Does a patient with a distracting injury, altered mental status, or pain require radiographic examination?
   1. Level I: There is insufficient evidence to support level I recommendations for the management guideline.
   2. Level II:
      a. Radiologic workup is indicated for high energy mechanism of (previously noted) injuries including the following:
         i. Altered mental status, evidence of intoxication with ethanol or drugs, distracting injuries, neurologic deficits, and spine pain or tenderness upon palpation.
      b. Multidetector CT scan with reformed axial collimation is superior to plain films in the screening of the TLS for bony injury.
   3. Level III:
      a. CT scan may be associated with less overall radiation exposure than plain films.
      b. Ligamentous injury without bony injury of the TLS is extremely rare. However, MRI is indicated for patients with neurologic deficits, abnormal CT scans, or clinical suspicion despite normal radiographic evaluation suggesting an unstable injury.
c. Plain films are adequate for the evaluation of the TLS if the patient did not require CT scan for some other reason.

C. Does the obtunded patient require radiographic examination?
   1. Level I: There is insufficient evidence to support a level I recommendation for the management guideline.
   2. Level II:
      a. Multidetector CT scan with reformatted axial collimation is superior to plain films for the screening of the TLS for bony injury.
   3. Level III:
      a. The obtunded patient, because of intoxication or closed head injury, presenting at a center without CT scan capability, should be transferred to the nearest available trauma center.

**Additional Recommendations**

1. Plain films are not recommended for the primary screening of the trauma patient with a major mechanism of injury as described previously, for clearance of TLS injuries. In a scenario where the patient does not have a major trauma mechanism (as defined above), altered mental status, or an indication for a CT scan to screen for other injuries, plain film may be used to screen for thoracolumbar (TL) injuries.

2. The use of CT scan for screening blunt trauma patients for TLS injuries as the only screening modality decreases radiation exposure, and decreases the time to diagnosis of an injury. Most blunt trauma patients commonly undergo CT scan of the head, chest, abdomen, and pelvis. Multidetector CT scans have the software capability to reformat bony images in addition to soft tissue during an initial radiographic examination.

3. For patients with neurologic deficits referable to a TLS injury, and particularly those with normal plain films, it is extremely important to obtain an MRI scan as soon as possible after admission to the Emergency Department. Early decompression of mass lesions, such as traumatic herniated discs or epidural hematomas, is also likely to improve neurologic outcome.

4. The ultimate evaluation of all radiographic studies will be the responsibility of attending radiologists. However, at-

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**Fig. 2.** Flow diagram thoracolumbar spine clearance.
tending trauma surgeons, emergency medicine physicians, neurosurgeons, and orthopedic spine surgeons are considered qualified to properly interpret TLS radiographs. Based on that interpretation, their clinical evaluation of the patient, and after proper documentation in the patients’ medical record, they may “clear” the TLS and remove TLS precautions.

**SCIENTIFIC FOUNDATION**

**Historic Background**

TLS injury remains a significant cause of morbidity and mortality in the trauma patient.\(^4,21\) The need for screening radiographs of the cervical spine is well recognized. Screening for cervical spine injury has been studied and analyzed, culminating in practice management guidelines by the EAST in 1998.\(^5\) Screening trauma patients for TL injury, in contrast, has not been studied as extensively and is the subject to more controversy.\(^1,6,7,16,18,19,24,25–28\)

Most clinicians would agree that radiographic evaluation of the spine should be obtained in patients with back pain, tenderness, or a neurologic deficit after blunt trauma,\(^1,16\) inability to perform an examination,\(^11\) altered mental status,\(^6,29\) multiple or distracting injuries, or the presence of other spinal fractures.\(^4,6\) Routine radiographic screening of alert, asymptomatic patients, however, is controversial.\(^11,12,18\)

Certainly, the absence of symptoms does not exclude injury to the TLS. Frankel et al. found that only 60% of trauma patients with confirmed TL fractures were symptomatic.\(^6\) Cooper et al.\(^1\) reported a review from Maryland’s Shock Trauma Center of 183 TLS fractures, in which 110 patients who were neurologically intact, with a Glasgow Coma Scale score between 13 and 15, and considered amenable to clinical examination. Thirty-four (31%) of these patients were recorded as having no pain or tenderness, yet all had fractures. The evidence would suggest that many of these fractures are not truly asymptomatic, but rather occult fractures because of the presence of intoxication or unreliable physical examination.

Fractures of the TLS have historically been diagnosed with the combinations of plain radiographs (anterior-posterior and lateral) and physical examination. Despite the difficulty in interpretation of these roentgenograms and the rate of missed injuries,\(^2,7,8,30,31\) plain radiographs are currently considered the gold standard for the evaluation of fracture to the TL spine.\(^7,31\) Screening criteria for the identification of TL fractures has been subject to wide variation among trauma centers. The current guidelines are intended to be used as standard practice in high-risk patients, to identify which patients require radiographic examination, and the study of such is most appropriate.

**Risk Factors for TLS Fractures**

Multiple mechanisms of injury are proposed as important risk factors for the development of TLS fracture. These factors include falls >10 feet, ejection from a motor vehicle, motorcycle crashes, high-velocity injuries, pedestrians struck by motor vehicles, and generalized tonic-clonic seizures.\(^6,12,14,16,19,32–36\) With few exceptions,\(^1,6,37\) however, the literature does not support radiographic screening on the basis of mechanism alone.

It is generally accepted that alterations in sensorium, either from head injury, shock, or intoxication, may mislead the physical examination.\(^1,6,10–12,14,16,19,38,39\)\(^1\) and all but two studies\(^16,18\) found that TLS fracture may be asymptomatic.

Multiple studies have documented the phenomenon of multilevel, noncontiguous spinal fractures, implying that a fracture identified in any region of the spine is an indication for full, radiologic spinal survey.\(^34,40–44\)

Nonspinal injuries are associated with TLS fractures, either as a distraction to physical examination or as a marker of mechanism severity.\(^4,14,16,19,37,39,44,45\)

Three prospective studies were reviewed. Terregino et al. found that in conscious patients with normal mental status and no distracting injury, the absence of back pain or tenderness had a 95% negative predictive value for TLS fractures.\(^11\) Holmes et al. and Frankel et al. defined screening criteria for TLS fractures and applied these criteria prospectively to 2,884 patients with blunt trauma mechanisms. The sensitivity and negative predictive value of their screening criteria was 100%\(^6,10\).

The literature supports no further workup in asymptomatic patients with normal mental status, no distracting injury, and normal physical examinations.

**Evaluation of the Evidence Supporting Screening With Plain Films**

There is little data to support using plain film radiographs to diagnose TLS fractures, although this has remained the radiologic gold standard by default.\(^15,46–48\) Despite this, plain films are likely adequate for screening with one caveat: any patient with risk factors for TLS injury that does not otherwise require transfer to a trauma center or CT scan for any other reason may be cleared with plain films.

**Evaluation of the Evidence Supporting Screening With CT Scan**

Use of CT scan for evaluation of injuries to the head, chest, and abdomen is common and considered routine for screening and diagnosis in trauma patients. It was inevitable that its use would expand to allow evaluation of the spine. Initially single-slice CT was used, where false detections in CT resulted from the difficulty in visualizing transverse fractures on first generation CT scans.\(^13,49\) As a result, CT was historically recommended as a complementary examination to plain radiography to assess the extent and stability of spinal fractures, or to visualize areas of the spinal axis where plain radiography was difficult to interpret, particularly the upper thoracic region and cervicothoracic junction.\(^50\)

First generation CT scans involve a single detector revolving around the patient. Helical CT scanning (second generation) allows continuous motion of both the detector and the patient, resulting in continuous spiral data collection.
The current multidetector helical CT scan (third generation), in which multiple detectors simultaneously collect source data volumetrically as the patient is advanced through rotating X-ray beams, currently affords fast and accurate data collection. Multidetector CT scans also allow reformating of images after collection, virtually minimizing false negative exams that plagued first generation CT scans.

The historic use of CT scans to evaluate TL fractures had been to identify poorly visualized areas of the spine or areas with questionable fractures seen on plain radiography. Ballock et al. and Fontijne et al., in separate studies from 1992, demonstrated the inadequacy of plain radiography in the diagnosis of TL fracture.13,31 The study of Ballock et al., in particular, is of concern because 25% of the patients in the study would have had missed fractures if plain radiography alone was used for imaging. In a prospective study from 2002, Gestring et al. used anterior and posterior and lateral scout films and axial images obtained in patients requiring abdominal and pelvis CT scan, and they compared these images with plain radiography.7 This study found 10 of 71 patients examined had TL fractures and the protocol rendered a 100% sensitivity and specificity in diagnosing fractures of the TL spine. Hauser et al., in 2003,8 prospectively studied 222 patients who required evaluation of the TL spine with both plain radiography, along with a helical CT scan (third generation) with 5 mm images. Thirty-six patients (17%) were found to have acute fractures of the TL spine. Accuracy of the CT scan was 99%, compared with an accuracy of 87% for plain radiographs. The CT scan was also able to identify acute versus old fractures.

Reformatted helical CT scan images were compared with plain radiographs by Sheridan et al. in 2003.2 This study reported the used 2.5-mm reformatted images. The reformatted CT scan of the chest and abdomen was accurate in screening for TL fractures. Sensitivity for thoracic fractures was 97% (compared with 62% for plain X-ray film). For lumbar fractures, sensitivity was 95% (compared with 86% by plain X-ray film). Roos et al. confirmed the accuracy of reformatted images in 2004, reporting a sensitivity and specificity of 98% and 97%.17

The current available data supports the use of current generation, multidetector CT scan in the screening of trauma patients for TL spine fracture. When multidetector helical CT scan of the chest, abdomen, and pelvis has been performed, evaluation of frontal and lateral scout films with the axial images or reformatted images can replace conventional radiographs of the TLS.2,7–9,51 Reformating of images allows a superior visualization of the spine and may be appropriate for areas of high concern.2,8,17

Routine CT scanning of the chest is not indicated for every injured patient. Selected patients who are at high risk for injury to the TL spine, however, can benefit from a CT scan, particularly if the CT scan is simultaneously used for evaluation of the chest and intra-abdominal organs. For patients with low energy mechanisms who require radiographic evaluation, plain radiography is likely sufficient. Areas of concern can be subjected to further examination by a CT scan, as needed. Concerns of radiation exposure have been addressed by Hauser et al.8 No excess radiation exposure was reported when integrated truckle CT scan was used, compared with organ and region-specific plain radiographs.8 This study also noted advantages in time to diagnosis and cost savings for the trauma patient by the elimination of plain radiography.

**Evaluation of the Evidence Supporting Indication for MRI**

Ligamentous injury of the TLS without bony injury is extremely rare.52–54 The indications for MRI of the TLS after blunt trauma are fractures with neurologic deficits, CT scan findings, and pain on clinical examination without radiographic abnormalities concerning for ligamentous injury.55,56 The TL “burst” fracture occurs approximately 14% to 48% of the time, and a neurologic deficit is present in 65% of patients. The soft tissue components of the injury including ligamentous disruption are not visualized with plain films or CT scan, and warrant early MRI.57,58

**SUMMARY**

There are no prospective, randomized studies of the use (or nonuse) of any single group of imaging studies for the early determination of TLS fractures or instability. Therefore, a level I recommendation cannot be made.

There are numerous prospective and retrospective cohort studies of large and small numbers of trauma patients, which provide insight into the incidence of TLS injuries after blunt trauma. Approximately 25% of patients meeting criteria for screening with CT scan after blunt trauma will have a TLS injury. Computer tomography imaging of the bony spine has advanced with helical and currently multidetector images to allow reformatted axial collimation of images into two-dimensional and three-dimensional images. As a result, bony injuries to the TLS are commonly being identified. Most blunt trauma patients require computer tomography to screen for other injuries. This has allowed the single admitting series of CT scans to also include screening for bony spine injuries. However, all of the publications fail to clearly define the criteria used to decide who gets radiographs or CT scans. No study has carefully conducted long-term follow-up on all of their trauma patients to identify all cases of TLS injury missed in the acute setting. Thus, the true incidence of TLS injury is not known.

It is clear from the literature that no imaging modality is 100% accurate of the time. Most studies have found that radiographs of the TLS (anterior-posterior, lateral) are commonly inadequate, especially in obese patients, providing only a sensitivity and specificity of 60% to 70%. With the currently advances in computer tomography, plain films play only a limited role in the initial screening for TLS injuries.
FUTURE INVESTIGATION

Future studies should prospectively evaluate and identify those imaging studies that should be utilized to make an acute determination of TLS injury and stability.

REFERENCES


A 69-year-old woman presented with right-sided flank pain, hypotension (90/56 mm Hg), and fever (38.4°C). She had a history of poorly controlled type 2 diabetes mellitus with evidence of chronic renal failure (creatinine: 7.4 mg/dL). A plain abdominal radiography showed a crescentic collection of air surrounding the right renal fossa (Fig. 1). Subsequent unenhanced computed tomography of the abdomen (Fig. 2) disclosed extensive destruction of the right kidney (asterisk) and a massive air collection within Gerota’s fascia (arrows) as well in the ureter (arrowhead) and urinary bladder, confirming the diagnosis of emphysematous pyelonephritis (EPN). The left kidney appeared smaller with irregular contour. Given the prediction of poor renal outcome, she underwent right-sided nephrectomy and received antibiotic therapy with intravenous meropenem. Cultures of blood, urine, and renal tissue grew *Escherichia coli*. She had an uncomplicated postoperative course and discharged on the 10th hospital day, but required life-long hemodialysis.

EPN represents a severe life-threatening infection of renal parenchyma with gas-forming bacteria.1,2 Optimal treatment regarding EPN is controversial, but the mortality rate in patients treated with antibiotic alone or accompanied by percutaneous drainage has been demonstrated to be equivalent to that of patients treated with radical nephrectomy.3,4 However, patients with a fulminant clinical course, unsuccessful drainage, or failed conservative therapy should undergo nephrectomy promptly to avoid a catastrophic outcome.

REFERENCES
Letters to the Editor

To the Editor:

We recently received a 27-year-old female zoo worker who was attacked by a jaguar (Panthera onca) while cleaning its cage. She arrived with vital signs, but was unresponsive with profusely bleeding bites to her neck and upper chest. She was immediately taken to the operating suite and we attempted to control the bleeding from thoracocervical vessels via a sternotomy with cervical extension. Although we controlled blood loss from the innominate and internal jugular veins, blood continued to emanate from her neck. We subsequently discovered a lethal, complete trans-section of her cervical spine, which caused uncontrollable bleeding from her vertebral vessels.

It is with great interest that we only found three published reports of survivors of severe attacks from these animals\(^1,2\) and learned that cervical spine injuries are not only common and should be investigated before determining salvageability (roentgenogram in trauma bay), but that this is the usual cause of death.\(^3,4\)

We wish to remind our colleagues that attacks from wild cats occur with some frequency in the United States, mostly against children and are commonly associated with unlicensed ownership of these underappreciated hunters.\(^1,3–4\) We hope this assists others in managing patients with injuries of this cause.

Guillermo A. Escobar, MD
K. Barry Platnick, MD, FACS
Department of Surgery and Trauma
Denver Health Medical Center
Denver, CO

REFERENCES

To the Editor:

We would like to comment on the article by Seamon et al.\(^1\) We are concerned that a casual reader of the abstract of this article could be seriously misled by its conclusions.

The authors claim that pyloric exclusion leads to a trend toward more complications, a higher pancreatic fistula rate, and a longer hospital length of stay, and they make the rather definitive statement that based on their data, “... the addition of pyloric exclusion to the repair of duodenal injuries provides no added benefit". Disregarding the fact that the difference in the outcomes measured was not statistically significant, and therefore, it is scientifically incorrect to base a conclusion on a "trend", the article suffers from a fundamental error.

The two groups, patients who underwent a pyloric exclusion and those who did not, are not comparable. The authors suggested that because the mean pancreatic injury grades were not statistically significantly different, the groups were similar. However, they failed to consider that of the 14 patients who underwent pyloric exclusion, 10 had pancreatic injuries whereas only 3 of the 15 patients who had not undergone exclusion had pancreatic injuries ($p = 0.009$; Fisher’s exact test).

Another interpretation of this data could be that, in patients with penetrating duodenal or combined pancreaticoduodenal injuries, pyloric exclusion performed for combined injuries leads to outcomes similar to those of patients having only duodenal injuries.

James E. Barone, MD, FACS, FCCM
Samual P. Kigongo, MD, FACS
Department of Surgery
Surgical Intensive Care Unit
Lincoln Medical and Mental Health Center
Bronx, NY

REFERENCES

To the Editor:

I have read with interest Abadal-Centellas et al.'s\(^1\) study regarding treatment of refractory intracranial hypertension and its control by means of external lumbar drainage (ELD). As a neurosurgeon, I have many reservations about using this method in these particular circumstances. I think that despite the results of this limited study, it is still unsafe to cause a pressure gradient by draining cerebrospinal fluid (CSF) from the lumbar area in these circumstances. If we go back to the 2001 Munch et al.\(^2\) study about the same issue, we find that two patients showed unilateral fixed and dilated pupils 6 hours and 8 hours after the lumbar drainage, indicating a temporary uncal herniation that was reversed when the drainage was stopped. Also in the study by Abadal-Centellas et al.,\(^3\) all patients who died but one presented with partially compressed cisterns, I believe this should make us think twice before inserting a lumbar drain.

External ventricular drainage (EVD) has been a popular way to control high intracranial pressure (ICP) in traumatic brain injury (TBI). I agree with the authors that its use in European centers is infrequent. This is because the idea of draining CSF to reduce ICP is not yet universally agreed upon as there is no randomized study confirming its impact on the outcome and not because of its infectious complications and limited using time as the authors indicated. A recent study by Lo et al.\(^3\) on a series of 199 patients with EVDs showed incidence of ventriculostomy-associated CSF infection is 10.6%. In fact, their analysis of 34 previous studies showed that the overall EVD-associated CSF infection rate was 6.9%. Lo et al. also found that
ventriculostomy infections are independent of drain duration and Abadal-Centellas et al.’s argument about its limited using time is not entirely accurate.

Refractory intracranial hypertension in traumatic brain injuries still represents a challenge to neurosurgeons, and currently, two major clinical trials (RescuICP in the United Kingdom, and DECRA in Australasia) about early decompressive craniectomy are ongoing. The management of high ICP in head injuries should always be based on multidisciplinary decision-making shared between the neurosurgeons and the neurointensivists.

Hazem Akil, MD, MRCSEd
Department of Neurosurgery
Wellington Hospital
Wellington, New Zealand

REFERENCES

The Authors’ Reply:
We appreciate the interest of Dr. Akil in our article published in the February issue of the Journal of Trauma. Dr. Akil raises concerns about the use of external lumbar drainage to control posttraumatic refractory intracranial hypertension (ICH), because he considers this to be an unsafe method. He cites the article by Münch et al., in which two patients presented a reversible mydriasis when cerebrospinal fluid (CSF) drainage was stopped. Because of this potential risk, he recommends thinking twice before inserting a lumbar drainage. We really do, as detailed in our study, a fact that is not acknowledged by Dr. Akil.

In summary, we don’t share Dr. Akil’s point of view. First, in our study, no patient presented pupillary abnormalities during the lumbar CSF drainage. Our protocol clearly specifies the management of the draining system depending on the ICH values, minimizing the potential risks. As in the study by Münch et al., the existence of certain radiologic conditions was mandatory, as was continuous neuromonitoring.

Second, the most important point is to really understand which patients are treated with lumbar CSF drainage. They were patients with traumatic brain injury (TBI) presenting with refractory ICH to second level measures. According to the traumatic coma data bank guidelines, these patients have an expected mortality of up to 84% to 100%. Therefore, we consider that the benefit obtained with lumbar CSF drainage clearly outweighs the risks in this subset of patients with refractory ICH.

Finally, we agree with Dr. Akil that ongoing studies in severe TBI evaluating decompressive craniectomy will help us to elucidate the best treatment in these patients. However, at this moment its use in this setting reaches the category of “option” in guidelines. Both neurointensivists and neurosurgeons must be aware of the benefits and risks of the treatment applied to TBI patients.

Josep M. Abadal-Centellas, MD
Juan A. Llompart-Pou, MD
Javier Homar-Ramírez, MD
Jon Pérez-Bárceca, MD
Hospital Universitario Son Dureta
Palma de Mallorca, Spain

REFERENCES

To the Editor:
In the May 2007 issue of The Journal of Trauma, Griffey et al. report on changes in thoracolumbar computed tomography (CT) and radiography use for trauma patients after deployment of multidetector CT in emergency rooms. The authors conclude that no evidence-based criteria currently provide clear direction as to whether acquired CT data should be reformatted for spinal imaging in every patient undergoing thoracolumbar CT examination. We respectfully question this conclusion.

Many large-scale studies in the current related literature state that reformatted CT images are more accurate than X-ray examinations for patients with spinal trauma. Various advantages of reformatted CT images in trauma patients had been addressed by Sheridan et al. as providing accurate screening while eliminating time loss, expense, and over-radiation exposure associated with X-ray examinations. Sagittal and coronal reconstructions of thoracic and lumbar spine are useful in improving sensitivity of spine fracture detection in trauma patients undergoing thoracoabdominal CT. Therefore, whether an abnormality is seen on axial images of a patient or not, sagittal and coronal reconstructed images should be evaluated to diagnose missed fractures in patients with increased risk of fracture secondary to the nature of the trauma mechanism (motor vehicle crashes, pedestrian struck, falls, etc.) and to delineate detailed analysis of present fractures. We think that, in patients with multiple injuries, after CT scanning there is no question on whether evaluating reformatted images is necessary, but criteria of imaging which patient is a debate.

In conclusion, we strongly disagree with the conclusion of Griffey et al. because we think that there are many studies proving various benefits...
of evaluation of reformatted images; we additionally suggest that isotropic data acquired via multidetector CT should be used for evaluation of each patient with multiple injuries.

Erhan Akpinar, MD
Baris Turkbey, MD
Department of Radiology
Hacettepe University School of Medicine
Ankara, Turkey

REFERENCES

The Authors’ Reply:
We appreciate the opportunity to respond to the comments from Drs. Akpinar and Turkbey as we feel that these comments miss our major points, which we acknowledge are somewhat nuanced and so might easily be misinterpreted. This communication provides an opportunity for us to clarify our findings and conclusions.

We agree on all points that for the multiply injured patients who warrant thoracolumbar spine (TLS) evaluation, CT is superior to X-ray in regard to sensitivity, specificity, and cost and time savings. Further, we do not question the routine use of sagittal and coronal multiplanar reformations (MPRs) of the chest, abdomen, and pelvis (CAP) as part of the prescribed diagnostic evaluation of the multiply injured patient with CAP imaging. These additional planes of imaging improve the screening evaluation of not just spine injury, but also for diaphragmatic, aortic, and a host of other potential injuries to structures oriented in the long axis of the torso. In fact, it is our routine practice to obtain these MPRs for all patients undergoing CT, including our nontrauma population. In our study, we differentiate routinely obtaining MPRs of the CAP (that would of course include the spine) from dedicated axial reconstructions and MPRs optimized to the spine (with smaller field of view limited to spine and thinner slice thickness); the latter is our concern. Even though both methods can be generated from the same acquired multidetector CT (MDCT) data set, dedicated axial reconstructions require additional time, energy, and effort that may not be warranted for every trauma patient.

Our main concern regarding utilization of MDCT for evaluation of TLS injury in trauma involved the finding that after MDCT deployment, CT did not simply replace radiography (as would be appropriate) among patients undergoing CAP evaluation and for whom TLS injury might be of clinical concern. Instead, utilization of MDCT for this indication was substantially increased above prior use of radiography, even after adjusting for changes in patient volume and severity. This suggests that TLS imaging was being ordered as an additional test among some trauma patients who previously would not have received TLS imaging at all. The reason for increased interest in TLS screening is unclear. We also noted a parallel significant increase in chest CT utilization during the study period. Our hypothesis (not tested in this study) is that the added ability to obtain thoracic spine clearance as part of a chest CT has led to a reflexive tendency to add chest CT to other imaging methods in trauma as part of a “pan scan” approach (rather than obtain thoracic spine films, if indicated, when TLS screening is desired in the absence of concern for intrathoracic injury). In fact, anecdotally, we frequently hear physicians comment that they want to scan the chest (often after a completely normal chest X-ray examination), to obtain images of the thoracic spine, despite no particular concern for intrathoracic injury. To our knowledge, there are no evidenced-based criteria for proceeding in this manner.

Although CT evaluation clearly improves sensitivity and specificity for TLS injuries, its liberal use in the absence of well-defined utilization criteria ignores important competing concerns regarding radiation dose, resource utilization, and timely throughput of trauma patients. Although our study does not question the value added by the routine use of MPRs performed as part of a CAP CT as outlined above, we do report and question the significantly increased utilization of MDCT over historic use of radiography for evaluation of TLS injury. These concerns must be considered before making clear and responsible recommendations for imaging strategies among trauma patients.

Richard T. Griffey, MD, MPH
Stephen Ledbetter, MD, MPH
Center for Evidence Based Imaging
Brigham and Women’s Hospital
Harvard Medical School
Boston, MA

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Regency La Joya Hotel–San Diego, CA. Fees vary ($350–$750). Information: Phone: (713) 965-0566; Fax: (713) 960-0488; Post: ASER Meeting Department, at ASER, 4550 Post Oak Place Suite 342, Houston TX 77027; E-mail: aser@meetingmanagers.com; Website: www.crad.org.

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Harvard Critical Care and Trauma Symposium.
Fairmont Copley Plaza Hotel–Boston, MA. Information: Contact 1–George Velmahos, MD, PhD, Phone: (617) 726-9591; E-mail: rmartinez3@partners.org; Website: http://massgeneral.org/trauma; Contact 2–Harvard CME, Phone: (617) 384-8600; Website: http://cme.med.harvard.edu.

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Emergency Medicine in the Developing World.
Cape Sun Hotel, Cape Town, South Africa. Information: Phone: +27 (0) 21 406 6407; Fax: 27 (0) 21 448 6263; E-mail: mcollin@curie.uct.ac.za; Website: www.emssa2007.co.za.

June 28–July 2, 2008
International Shock Congress.
Gürzenich Convention Center, Cologne, Germany. Fees vary (€40–€570). Information: Post: Edmund A.M. Neugebauer, PhD, University of Witten/Herdecke, Professor and Chairman of Surgical Research, Institute for Research in Operative Medicine, Ostmerheimer Str. 200, 51109 Cologne, Germany; E-mail: science@shock2008-cologne.org; Website: http://www.shock2008-cologne.org.
Complete Absence of the Pericardium in a Patient With Multiple Injuries

Douglas W. Green, MD, Bryan F. Meyers, MD, Sanjeev Bhalla, MD, and Bruce L. Hall, MD, PhD, MBA

Congenital pericardial defects are rare; fewer than 200 cases have been reported in the literature. These defects are usually asymptomatic, often presenting only at autopsy, with an approximate rate of 1 in 14,000 cases. These defects, however, may result in serious complications, including cardiac herniation and subsequent muscle incarceration, occlusion of venous inflow, and compression of the coronary arteries. Defects of the pericardium are thought to result from errors in the formation of the pleuropericardial membranes, most likely caused by inappropriate early atrophy of the ducts of Cuvier, which supply blood to the developing pleuropericardial membranes. In most instances, these defects are left-sided. Right-sided defects and complete absence of the pericardium are extremely rare; the right duct of Cuvier forms the superior vena cava, usually ensuring that the developing right pleuropericardial membrane has an adequate blood supply.

We report the case of a 45-year-old man with multisystem trauma and several radiographic abnormalities of the chest that initially could not be explained. He ultimately proceeded to surgery and was found to have complete absence of the pericardium.

CASE REPORT

A 45-year-old man whose medical history consisted solely of alcohol and drug abuse was transferred to the Washington University-Barnes Hospital Emergency Department in critical condition after being struck as a pedestrian by an automobile traveling at a high rate of speed. At the scene, he was hypotensive, combative, and confused. He was initially evaluated at another hospital where he was found to have a left scapular fracture, left rib fracture, left pubic ramus fracture, and gross hematuria, but was otherwise stable. He was transferred to our hospital for further management. Upon arrival, he was alert but confused, with labored respirations. Primary survey revealed a head laceration with multiple abrasions and multiple bilateral anterior contusions of the chest with numerous areas of crepitus and tenderness. He had breath sounds bilaterally. The abdomen was soft and non-tender. His pelvis was tender but stable. Secondary survey revealed diminished left-sided breath sounds. Oxygen saturation registered in the low 80% range despite full-mask oxygen. Foley catheter placement revealed gross hematuria. Chest radiograph demonstrated bilateral pneumothoraces, bilateral rib fractures, pneumomediastinum, and apparent pneumopericardium (Fig. 1). He was intubated and bilateral chest tubes were placed, resulting in improved oxygenation. Computed tomography (CT) of the head was unremarkable, and an abdominal/pelvic CT demonstrated two small liver lacerations, a focal suprarenal abdominal aortic dissection, and a pelvic hematoma with active extravasation. Chest CT demonstrated bilateral rib fractures, extensive subcutaneous emphysema, bilateral pneumothoraces, and extensive pneumomediastinum and continued apparent pneumopericardium despite chest tube placement (Fig. 2). After aggressive fluid resuscitation, angiography was performed. This revealed brisk bleeding from the left obturator artery, which was embolized, and an insignificant focal dissection of the suprarenal abdominal aorta. The patient was transferred to the surgical intensive care unit for further management.

During the next several days, the patient remained in critical condition, with repeated episodes of oxygen desaturation, and continued evidence on chest radiograph of bilateral pneumothoraces and pneumomediastinum. These did not respond to placement of an additional chest tube on the left side. On hospital day 7, the patient became hypoxic and hypotensive. Absent breath sounds over the left chest led to needle decompression with immediate improvement of the patient’s oxygenation and hemodynamics. Subsequently, an additional left chest tube was placed. Follow-up chest radiograph suggested pneumopericardium and a persistent left basilar pneumothorax. Electrocardiogram demonstrated sinus rhythm with a substantial decrease in voltage compared with that of earlier studies. A transthoracic echocardiogram was limited by air-acoustic interference anteriorly. This made obtaining parasternal windows futile. Subcostal views dem-
onstrated normal left ventricular (LV) function without pneumopericardium or pericardial effusion.

The patient’s substantial ventilator requirement persisted, as did his left-sided pneumothorax. He developed a collapsed left lower lobe, despite multiple chest tubes and frequent bronchoscopy. Ultimately, the Division of Thoracic Surgery was consulted and they recommended a left thoractomy to further elucidate the nature of the conditions. During the operation, the collapsed left lower lobe was found encased with a fibrinous peel and loculated effusion, which responded to decortication. An unanticipated finding was the absence of a pericardium, resulting in a common pleural space and complete communication between the left and right chest. Despite thorough examination, we found no pericardial remnant that might be expected after pericardial rupture, strongly suggesting the congenital absence of the pericardium. This absence was thought to account for the erroneous interpretation of pneumomediastinum and persistent pneumopericardium on previous radiologic studies (see figures), and might possibly have resulted in bilateral pneumothoraces when only a left-sided lung injury existed. After the patient’s anatomy was known, review of the original plain radiographs revealed a tongue of lung tissue interposed between the main pulmonary artery and aorta, a finding not previously appreciated, and consistent with congenital absence of the pericardium.

The patient made a slow recovery with no further acute issues. His chest tubes were removed without recurrence of pneumothorax, and he was weaned from the ventilator. The remainder of his hospital course was unremarkable.

**DISCUSSION**

Pericardial defects are rare and are unlikely to cause symptoms. Additionally, if they are suspected, confirmatory diagnostic imaging can be quite challenging. Plain chest films can suggest the diagnosis of a pericardial defect, but more frequently, echocardiography and CT or magnetic resonance imaging have been used to establish the diagnosis. However, the presented case demonstrates that modern modalities can be unsuccessful and the diagnosis might only be confirmed upon surgical exploration.

By his report, this patient had had no symptoms referable to his pericardial defect before the collision. However, the complete absence of the pericardium may help to explain his severe respiratory difficulty on presentation. Absence of the pericardium resulted in the formation of a single pleural space. His left-sided lung injury therefore likely resulted in life threatening bilateral pneumothoraces. This condition has been previously referred to as a “buffalo chest”, as a common pleural space is often found in North American Buffalo. It was apparently well known by Native Americans that the single pleural space in these animals allowed them to be relatively easily killed by a unilateral chest wound (i.e., an arrow causing sudden bilateral pneumothoraces).

Additionally, the absence of pericardium led to the erroneous interpretation of the chest films as showing pneumopericardium and pneumomediastinum. Before the availability of current imaging modalities, pericardial defects were often diagnosed by chest radiography after first injecting air onto the pleural space on the side of a proposed pericardial defect. The air would then outline the pericardium and define any possible defects, as occurred inadvertently in this patient.
Aside from the increased risk of bilateral pneumothoraces in patients with complete absence of the pericardium, patients with partial defects have a greater risk of morbidity. Herniation of the heart through a partial defect can result in incarceration of that segment and ultimately strangulation of the tissue or even death of the patient. However, the significant majority of pericardial defects do not require intervention. The management of symptomatic defects can be achieved through several means. Most can be safely treated by extending the defect with a longitudinal pericardiotomy. Primary closure, partial pericardectomy, or patch closure, with porcine or bovine pericardium or polytetrafluoroethylene have also been performed. This situation is expected to remain a very rare complicating factor in trauma.

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Concurrent Carotid Rupture and Coronary Dissection After Blunt Chest Trauma

Michael T. Pawlik, MD, Holger O. Kuenzig, MD, Stephan Holmer, MD, Peter Lemberger, MD, Karin Pfister, MD, Andreas G. Schreyer, MD, and Piotr Kasprzak, MD


This case report illustrates the importance of diagnostic measures of supraaortal vessels after blunt chest trauma. A high index of suspicion should be maintained in the posttraumatic period to detect injuries of carotid vessels as early as possible, especially in the anesthetized patient.

Traumatic arterial dissections are relatively rare incidents. Reviewing the literature revealed only 14 cases of traumatic coronary artery dissections that have been described within the last two decades. Traumatic lesions of the carotids are more frequent. Nevertheless, to the best of our knowledge no case of simultaneous traumatic coronary and carotid rupture has been described until now. We report a case of a 21-year-old man suffering from both coronary dissection and carotid rupture after a frontal impact car crash.

Case History

A 21-year-old male automobile driver had a frontal crash against a tree. His seatbelt was not fastened at the time of crash and the airbag on the driver’s side had not inflated. On arrival of the emergency physician, the Glasgow Coma Scale (GCS) score at the scene was 12 and quickly improved to 15 ten minutes later. Except for a slight disorientation he was fully awake and showed no neurologic abnormalities. Oxygen saturation and arterial blood pressure were in the normal range throughout the emergency treatment and during the hospital transport. Mild sedation with 7 mg of midazolam was administered to reduce restlessness during transport. For volume resuscitation, a total of 1,000 mL colloids and 1,500 mL of crystalloids was infused.

After 1 hour, the patient reached the emergency department having stable vital signs. Because of agitation and a presumed thoracic trauma, he was anesthetized and mechanically ventilated. While inserting a central venous line ventricular fibrillation occurred and was reconverted to sinus rhythm by a single 200-J electric shock. After this incident vasopressor treatment (0.4 mg/h of norepinephrine) was needed for circulatory stabilization. The thoracic computed tomography (CT) scan exhibited a bilateral lung contusion and a mediastinal hematoma. A right-sided pneumothorax was subsequently drained by a thoracic tube. The cranial CT showed minimal frontal contusions and a left ocular injury consisting of glass-splinter impact, retro bulb hematoma, and orbital fracture. The abdominal scan displayed no pathologic finding. Because of the eyeball lesion, he was brought to our university hospital by helicopter 8 hours after the crash for ophthalmologic treatment.

The electrocardiogram at admission in the emergency room showed ST segment-elevations in V3 to V5 and a loss of the R-wave in V2 to V6 (Fig. 1). At this time, the myocardial isoenzyme of creatinine kinase (CK-MB) was already elevated to 97.7 U/L with a total creatinine kinase (CK) of 768 U/L. Troponin I was raised to 7.65 ng/mL. Transthoracic echocardiography revealed both an anteroseptal hypokinesia and a septal akinesia. Coronary angiography showed an occlusive dissection of the proximal left anterior descending artery (LAD), while other coronary arteries were not affected (Fig. 2A). A percutaneous transluminal coronary angioplasty was performed and two stents were inserted, resulting in a complete reperfusion (Fig. 2B). Anticoagulation therapy using clopidogrel 75 mg/day, acetylsalicylic acid 100 mg/day, and enoxaparine 30 mg/day was administered. During the first three days after myocardial infarction, short episodes of ventricular tachycardia were encountered, but disappeared after antiarrhythmic therapy with amiodarone.

Because of the coronary dissection resulting from deceleration trauma we screened all supraaortic arteries for injuries by duplex Doppler ultrasonography. The right internal carotid seemed to have a second lumen, exhibiting arterial flow pattern. Because a dissection or rupture could not safely be ruled out, a helical angiography CT scan of the aorta and the supraaortic vessels and a cerebral CT was performed to visualize extracranial arteries and possible cerebral infarction in one session. CT angiography revealed a false aneurysm of the...
right internal carotid artery with a diameter of 1 cm and a length of 4 cm reaching up to the base of the skull (Fig. 3A), which was additionally confirmed by a preoperative digital subtraction angiography (Fig. 3B). Up to this time no clinical signs of cerebral infarction could be observed.

On the following day, the aneurysm was completely resected and a part of the saphenous vein was interposed. Patency of the right internal carotid artery was confirmed by postoperative subtraction angiography (Fig. 3C) and cerebral infarction was additionally excluded by a cranial CT scan. The patient was mechanically ventilated for a total of 4 days, for 2 of them lying in a rotating bed because of his lung contusions. Initially he needed high doses of catecholamines to support cardiac performance. Catecholamines were gradually reduced and stopped on day 4 after admission. An echocardiogram at this time demonstrated a normal left ventricular pump function with only a minimal septal dyskinesia. Eventually he left the intensive care unit in stable cardiopulmonary condition having neither a general nor a focal neurologic deficiency. Even his left eye had recovered completely without vision reduction. The patient was in normal neurologic and cardiac condition at follow-up 12 weeks after the trauma.

**DISCUSSION**

Blunt thoracic trauma can result in a wide variety of vessel injuries. The incidence of reported vessel injuries after blunt chest traumas has increased during the last two decades, probably because of improved diagnostic means. Coronary artery injury resulting from blunt chest trauma most often affects the left anterior descending artery and usually results from frontal impact motor vehicle crashes. Dissection of the coronary arteries with subsequent thrombus for-
Information is one of the possible pathophysiologic mechanisms of myocardial ischemia (MI) after blunt chest trauma. The early indicator of MI may be precipitous chest pain in the awake patient, whereas in an anesthetized patient ischemia may be difficult to diagnose. Electrocardiographic abnormalities such as ventricular arrhythmias and ST-segment alterations should be considered as specific signs of cardiac trauma. Echocardiography may show wall motion abnormalities, but coronary angiography is the diagnostic tool of choice to prove coronary dissection and simultaneously allows successful treatment with angioplasty and stenting. Because of early intervention, the patient had only slight impairment of cardiac function at discharge from the intensive care unit, despite a significant increase in cardio-specific enzymes CK-MB and troponin I. Thus, early transfer of such patients to hospitals that provide interventional cardiology is an essential requirement for the successful therapy of coronary complications.

Although coronary dissection causes electrocardiogram alterations or arrhythmias and thus can be detected even in the anesthetized patient, early diagnosis and successful management of traumatic carotid artery dissections are more difficult because of the lack of early symptoms. Dissection of the carotid artery after blunt head or neck trauma is more often reported than rupture and most frequently (greater than 90%) affects the extracranial internal carotid artery. It typically occurs in automobile crashes as a result of rapid deceleration, with resultant hyperextension and rotation of the neck. It is important to diagnose carotid dissections early after the trauma, because cerebral ischemia occurs in approximately 70% of all cases after traumatic dissection, either as transient ischemia attacks in 20% to 30% or as completed stroke in 40% to 60% of all cases. Symptoms in the awake patient include head or neck pain (75% of cases) or ipsilateral Horner’s syndrome (50% of cases), but the onset of symptoms can vary between hours and weeks after carotid artery injury.

In the multiply injured and anesthetized patient, symptoms are usually absent or masked. Only specific screening examinations may lead to early diagnosis before the occurrence of cerebral ischemia or stroke. Thus, even in an era of cost containment, resources should be targeted to individuals with upper body injuries caused by deceleration traumas. Duplex Doppler ultrasonography may be used as a first screening tool, but diagnostic sensitivity is limited by subtle dissections or an inadequate image of the carotid vasculature at the skull base and above. In our patient, the duplex Doppler ultrasonography led to suspicion of a carotid dissection or rupture, and was therefore followed by a helical CT angiography which confirmed rupture and false aneurysm of the right carotid artery. Patients are typically jeopardized by rupture, hemorrhage, thrombosis or embolism of the dissected carotid artery and there are several therapeutic options including observation, anticoagulants, antiplatelet agents, stenting and vascular surgery. Anticoagulation with heparin is commonly used as first line treatment for dissections although not evidence-based, but restrictions exist in patients with systemic or local traumatic injuries, as seen in our patient with retro-bulb hematoma and cerebral contusion. However, we decided to administer low molecular heparin after coronary stenting, while weighing the risk of stent occlusion and intracerebral bleeding. Early surgical revascularization is an additional option in traumatic carotid injuries and requires no systemic heparinization therapy, which is favorable in multi-trauma patients. Especially in patients with carotid rupture and aneurysm, formation revascularization is the option of choice.

Fig. 3. Computed tomography angiography (A) and digital subtraction angiography (B) showing rupture and false aneurysm of the right carotid artery preoperatively (arrow). (C) Successful surgical revascularization with a saphenous graft postoperatively (arrows).
because of the greater bleeding risk with anticoagulants. In this case, the treatment approach of coronary stenting and carotid bridging proved to be the optimal therapy and led to a favorable outcome.

CONCLUSION

The combination of coronary and carotid rupture after blunt chest trauma is unique, and could result in severe acute and chronic sequelae such as myocardial infarction and stroke.

This report emphasizes the importance of the early decision to transport patients with blunt chest trauma to hospitals with all diagnostic and therapeutic options of interventional cardiology and vascular surgery, as well as the importance of an interdisciplinary management of such patients.

In particular, this case suggests that there may be an association between these injuries after blunt chest trauma and we suggest further evaluation, especially in the anesthetized patient.

REFERENCES

Post-Traumatic Myocardial Infarction Complicated With Left Ventricular Aneurysm and Pericardial Effusion

Young Won Yoon, MD, SungHa Park, MD, Sang Hak Lee, MD, Minho Cho, MD, Bumkee Hong, MD, Dongsoo Kim, MD, Hyuck Moon Kwon, MD, and Hyun-Seung Kim, MD

J Trauma. 2007;63:E73–E75.

In patients with blunt chest trauma, the rate of cardiac injury is reported to be around 15%.1 Clinically significant injuries include cardiac rupture, valvular dysfunction, and coronary thrombosis, which present as tamponade, hemorrhage, or severe cardiac dysfunction. Patients suffering from major trauma are usually managed in the Intensive Care Unit (ICU) setting with myriads of medical problems. More often than not, blunt trauma of the heart may occur unnoticed or symptoms may be attributed to chest wall trauma or myocardial contusion and managed conservatively. The delay in diagnosis may result in serious manifestations of cardiac injuries days or weeks after the initial injury.2,3 Traumatic coronary artery dissection and occlusion is a rare complication of chest trauma that may manifest as acute myocardial infarction (MI). Here, we describe a case of a woman who sustained blunt chest trauma in a motor vehicle crash. She experienced acute MI resulting from coronary artery dissection complicated with left ventricular (LV) aneurysm and pericardial effusion, which gave rise to delayed clinical manifestations of decompensated heart failure 4 weeks later.

CASE REPORT

A 61-year-old woman sustained chest trauma during a motor vehicle crash. Initially, she complained of anterior chest pain and was mildly dyspneic. She had a medical history of essential hypertension and type II diabetes mellitus for 5 years, and had been well controlled by oral medications. Her vital signs at admission revealed blood pressure of 140/90 mm Hg, pulse rate of 103/min, respiratory rate of 22/min, and body temperature of 36.5°C. Initial chest examination revealed decreased breathing sound without rales or wheezing on both lung fields. Heart sounds were audible, but consistently distant, most likely because of the obese body habitus. The initial chest roentgenogram demonstrated multiple rib fractures and borderline cardiomegaly. There was left side pleural effusion which was because of traumatic hemothorax. Echocardiogram (EGC) showed sinus tachycardia without ST segment change (Fig. 1A). Results of the initial laboratory tests including cardiac enzymes were within the reference range.

Initial managements were closed thoracostomy for the hemothorax with otherwise conservative management for the multiple rib fractures. The hospital course was uneventful until 4 weeks after the admission when she complained of worsening dyspnea with development of pulmonary edema and generalized edema. Her blood pressure was 100/60 mm Hg and the heart rate was 100 bpm. The chest examination showed decreased heart sound without changes in the pattern of the breathing sound. Follow-up chest roentgenogram showed markedly increased cardiomegaly and the follow-up ECG revealed reduced amplitude of QRS and newly developed ST elevation and Q wave in anterior and inferior leads (Fig. 1B). Alterations in the clinical and ECG features led to the performance of echocardiography, which showed LV aneurysm at the entire cardiac apex with wall thinning (Fig. 2A). The global LV systolic function was markedly reduced (ejection fraction, 28%) with akinesia of the anterior wall, septum, and inferior segments from lower mid LV to apex. Moderate amount of pericardial effusion was noted mostly at posterior side with respiratory variation of mitral inflow Doppler examination and diastolic right ventricular collapse (Fig. 2B). Coronary angiography was subsequently performed that showed total occlusion of the distal left anterior descending (LAD) because of traumatic dissection of mid LAD (Fig. 3A, B).

After stabilization with medical therapy, the patient showed overall clinical improvement and remained hemodynamically stable. Although LV aneurysmectomy was planned as the next step of treatment, the patient refused the operation. She was discharged 1 month later and is being followed up at our out patient clinic and is doing well without any symptoms or complications.
DISCUSSION

The majority of blunt cardiac injuries are myocardial contusions. Other injuries from blunt trauma include myocardial aneurysm, valvular insufficiency, septal defect, and coronary artery injury. The mechanism of cardiac injury from blunt trauma can be either direct compression between the sternum and the vertebral column, or sudden increase in the intrathoracic pressure from abdominal and lower extremity

Fig. 1. (A) ECG at admission shows sinus tachycardia and LV hypertrophy without ST segment abnormality. (B) ECG 1 month later revealed reduced QRS voltage in limb leads, abnormal Q wave and poor R progression in precordial leads.

Fig. 2. (A) ECG findings of apical four-chamber view shows aneurysmal change from mid portion of LV to apex. Moderate amount of pericardial effusion was noted. (B) Parasternal short-axis view at lower mid LV level shows LV aneurysm with wall thinning except posterolateral segment. Pericadial effusion and pleural effusion were also noted.

Fig. 3. The angiography of left coronary artery shows development of traumatic dissection at the mid LAD (arrow) that tapered to a total occlusion of the distal LAD artery. (A) LAO cranial view. (B) RAO cranial view.
compression. Coronary artery injury resulting from nonpenetrating chest trauma is rare, but may be associated with significant risk of mortality from myocardial infarction.3–7 The proposed causes of acute myocardial infarction after blunt chest trauma include a variety of injuries to coronary arteries, such as laceration, thrombosis, intimal dissection, arteriovenous fistula, and pseudoaneurysm.8,9 Among them, intimal dissection has been the main suspect in the pathogenesis of coronary occlusion after trauma. Coronary artery dissection is defined as an intramural hematoma of the vessel wall (false lumen), which flattens the true lumen, leading to blood flow obstruction and acute myocardial ischemia in the absence of trauma or iatrogenic causes.10 In our patient, the culprit coronary artery showed linear dissection from the mid LAD that was tapered to a total occlusion of the distal LAD. Based upon the patient’s history of severe chest trauma, the diagnosis of traumatic coronary artery dissection was made. The possibility that the coronary artery dissection occurred spontaneously is very unlikely in this patient when considering the fact that the patient had a history of severe chest wall trauma and the fact that the majority of spontaneous coronary artery dissections occur in young females with a mean age of 40 years, particularly during late pregnancy and postpartum period.

Most ventricular aneurysms that follow blunt chest trauma are true aneurysms (wall formed by the scarred myocardium), in contrast to pseudoaneurysms (hematoma from ventricular rupture contained by pericardium) that commonly follow penetrating trauma. True aneurysm can be from either transmural myocardial contusion and necrosis or trauma-induced thrombosis of the coronary vessels causing ischemic damage to myocardium.11 The presentation of these aneurysms may be delayed and present anytime after the injury.12 In this case the symptom of MI was masked by chest trauma, and that of LV aneurysm and pericardial effusion became evident only after 4 weeks after admission. Pericardial effusions are more common in patients with anterior MI and with larger infarcts and when congestive heart failure is present.13 The majority of effusions after MI do not cause hemodynamic compromise, unless ventricular rupture or hemorrhagic pericarditis is combined. Early effusions are associated with edema and inflammation and late effusions tend to be a part of Dressler’s syndrome (postmyocardial infarction syndrome).14 In addition to MI, Dressler’s syndrome has been described after a variety of cardiac injuries including chest trauma.15 In the current case, the effusion was probably caused by MI and subsequent heart failure, and post-myocardial infarction syndrome could be partially associated. Symptoms and signs of cardiac injury may be overshadowed by the more evident manifestations of bone, great vessel and abdominal or extremity trauma. Therefore, patients with chest trauma should be followed up and re-examined to detect these important pathological findings. Follow up is important even if the initial assessment for injury is negative in those patients with significant traumatic chest wall injury.

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Kitesurfing: When Fun Turns to Trauma—The Dangers of a New Extreme Sport

Willem R. Spanjersberg, MD, and Inger B. Schipper, MD, PhD

A round the world a new sport is becoming more and more popular among “extreme sports” enthusiasts; kite-surfing. This sport combines parts from several existing sports like windsurfing, kite flying, and water-skiing. Using a small surfboard and a kite, surfers can achieve great speeds, and heights of over 20 m or 65 feet (Fig. 1). When falling or hitting something at this speed and height, the risk of damage to both equipment and surfer is obvious. The rising popularity has been accompanied by a growing number of accidents resulting in, sometimes very serious, injuries and even death. This has caused growing concern among authorities about the sport’s safety. Another concern entails the growing health care expenditure. Rising costs are caused in part by the dispatch of the helicopter emergency medical services (HEMSs), their treatment and retrieval of patients, and extensive in-hospital treatments.

A search in PubMed produced only two articles regarding injuries related to kitesurfing.1,2 Both the rising popularity and the suspected high risks the sport carries, suggest a major increase in the number of incidents and accompanying injuries for future years.

To objectify the presumed severity of kitesurfing-related injuries, we analyzed injury mechanisms, risk factors, and actual injuries sustained by kitesurfers who were injured severely enough that HEMS dispatch was warranted. In the Netherlands, the HEMS, called the Helicopter Mobile Medical Team, comprises a registered nurse from one of the ambulance services and a specially trained physician (anesthesiologist or trauma surgeon) from a Level I trauma center. This team can be dispatched from dawn till dusk and assists EMS personnel in the care of severely injured patients. One of the added values of this team is that they can perform medical interventions that a registered nurse is not able to or not allowed to perform.

The Sport

More and more athletes are taking up kitesurfing, and international competitions are being held all around the world. A growing number of companies are producing and innovating surfing equipment, while implementing more safety-enhancing features in boards and kites. To understand the mechanisms of injuries sustained, one must first look at the sport, including the accompanying risk factors.

Kitesurfers use a small surfboard and a kite. The kite is connected to the surfer by a harness and conveys wind energy to the board, thus facilitating motion. By changing his position to the kite or by changing the kite’s position to the direction of the wind, the surfer can swiftly change direction, perform turns, and make jumps (Fig. 1).

Three types of boards are generally used in kitesurfing. Every board has its own characteristics, and the choice for a particular one is usually made according to circumstances, user experience, or both. The first type is the directional board. As the name suggests, maneuverability is limited to one direction because of the presence of a wake. Every change in direction must be made by turning the board, which of course prohibits fast changes in course. However, the directional board provides more buoyancy; thus enabling the surfer to use the board as a flotation device in case of emergency. The second type is the bidirectional or “twin-tip”. This type is shorter than the directional board and has one or more fins on both sides, which makes it possible to change directions without changing the board’s direction. The third and smallest type is the wakeboard, which is also bidirectional and is known from water-skiing.

A number of different kites are also in use, varying in size and shape. Wind characteristics of each kite are roughly defined by the profile (or shape) and the “aspect ratio”. The profile describes the curving of the fabric. An increase in curving results in an increase of the amount of wind trapped by the kite, which generates more tension and force, called “pull”. More curved kites provide better stability and require less wind, but at high wind speeds they may produce too much force for the surfer to handle.
The aspect ratio is the ratio between the width and height of the kite (Fig. 2); a narrow but high kite means a low aspect ratio, providing stability and better control. A high aspect ratio means more speed and, combined with more curving, facilitates higher and more radical jumps.

The surfer can control the kite using a control bar, which is connected to the kite by two to five lines (Fig. 3). These lines have a diameter of about 1 mm and are made of very strong nylon-like materials.

Besides controlling the kite, the control bar serves another purpose; the so-called depower system, which enables the surfer to reduce the amount of wind trapped by the kite in strong winds. Also attached to the control bar is the quick release system, enabling a kite to be released quickly in case of an emergency, resulting in loss of power and hence propulsion of the board.

By analyzing the sport and the materials and techniques used, three main groups of risk factors were defined: material-related, speed-related, and height-related.

These risk factors can result in four main types of trauma mechanisms:

- Cuts and bruises owing to sharp edges and ropes or rocks.
- High-energy trauma owing to frontal collision.
- High-energy trauma owing to falls from height, i.e., vertical deceleration trauma.
- Drowning.

The latter three are considered potentially serious enough for an emergency dispatcher to dispatch the HEMS. The present study assessed the seriousness of injuries sustained during kitesurfing, for kitesurfers treated by Rotterdam’s HEMS in the past 3 years. This resulted in five documented cases.

**CASE REPORTS**

A summary of injuries of all five patients is given in Table 1 and the weather conditions and mechanisms of trauma are given in Table 2. The first case concerns a 41-year-old man. After a gush of wind, he lost control of his kite, was lifted up into the air, and thrown to the ground from a
height of approximately 10 m (or 30 ft). After hitting the ground a number of times and being dragged for 10 m, he came to a halt.

Prehospital and emergency department assessment led to the advanced trauma life support (ATLS) findings listed in Table 1. The patient had sustained a dislocated right shoulder, a laceration on his right elbow, and a complicated comminuted fracture of the right patella with partial deglovement of the right knee. He had also sustained a subtotal amputation of the third and fourth toe on his right foot along with cuts on the left foot, left knee, and frontal scalp. A computed tomographic scan showed stable fractures in the spinal processes of C6 and C7.

The second patient was a 30-year-old man who was lifted out of the water and, after flying a distance of about 20 m, was thrown against a billboard. The ATLS survey produced the findings listed in Table 1. Assessment revealed no fractures or any neurologic deficits, and the patient was admitted to the neurology ward for observation. Thirty minutes after admission, the patient displayed a sudden onset aphasia and became dysarthric. Central paresis of the right facial nerve with loss of sensation was also observed. Another 30 minutes later, physical examination revealed paralysis of the lower right arm, along with decreased deep tendon reflexes. The right leg also displayed a loss of sensibility, without loss of motor functions. Computer tomography-angiography (CT-A) showed bilateral dissection of the internal carotid arteries, along with left frontal lobe ischemia. The dissection was treated with heparin, and the frontal lobe ischemia resulted in extensive behavioral problems.

The third patient was surfing close to shore, when the wind picked up strength. After losing control of his kite, he was thrown over a dyke, and landed against a parked car. His main injuries consisted of a dislocated right shoulder, a fractured right femur, and a laceration of the face.

The fourth patient was thrown onto the beach from a height of about 4 m and landed on his right side. Other than a painful right chest, no injuries were found.

The last patient was a 40-year-old man who, on a stormy morning, was walking toward the waterfront and lost control of his kite after it was caught by a sudden gush of wind. He was thrown face first against a wooden pole, which extended above the sand. The patient sustained serious injury to his face and skull. On HEMS’s arrival the flight physician found the patient with a severely deformed maxillofacial area causing an obstructed airway. The cranium was also severely deformed, and both pupils were enlarged and unresponsive to light. There was neither breathing nor a palpable pulse. Because of the extent of his injuries, no attempts at resuscitation were made, and the patient was pronounced dead at the scene.

### Table 1 Patient Characteristics, Injuries, and Vital Signs

<table>
<thead>
<tr>
<th>Pt</th>
<th>Airway</th>
<th>Breathing</th>
<th>Circulation</th>
<th>Disability</th>
<th>Exposure</th>
<th>ISS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Clear</td>
<td>SO₂ 99%</td>
<td>P 69/min; BP 160/100</td>
<td>GCS 15; RTS 12</td>
<td>Open fracture right leg; luxation right shoulder; bleeding wounds head/neck/abdomen</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Clear</td>
<td>SO₂ 98%</td>
<td>P 95/min; BP 150/100</td>
<td>GCS 14; RTS 12</td>
<td>Distal femur fracture; dislocation right humerus with avulsion fracture tuberculum major</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Clear</td>
<td>SO₂ 99%</td>
<td>P 90/min; BP 160/90; LOC 20 mins</td>
<td>GCS 10; RTS 12</td>
<td>Bleeding wound upper left arm; tingles left hand; severe neck pain; bilateral carotid dissection</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Clear</td>
<td>SO₂ 100%; painful right thorax</td>
<td>P 75/min; BP 140/90</td>
<td>GCS 15</td>
<td>Nausea</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Obstructed by blood/fracture</td>
<td>None; SO₂ 84%</td>
<td>No P</td>
<td>GCS 3</td>
<td>Massive destruction of cranium and brain and fractured maxilla</td>
<td>75</td>
</tr>
</tbody>
</table>

Pt, patient; ISS, Injury Severity Score; SO₂, blood-oxygen saturation; P, pulse; BP, blood pressure in mm/Hg; LOC, loss of consciousness; GCS, Glasgow Coma Score; RTS, Revised Trauma Score.

### Table 2 Weather Conditions and Mechanism of Trauma Surrounding the Accident Per Individual Case Presented

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mechanism of Trauma</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Thrown to ground from height</td>
<td>Strong winds with sudden gushes</td>
</tr>
<tr>
<td>2</td>
<td>Flew through the air for 20 m, collided with a billboard</td>
<td>Undocumented</td>
</tr>
<tr>
<td>3</td>
<td>Thrown against a dyke, landed against a car</td>
<td>Strong winds, rainy</td>
</tr>
<tr>
<td>4</td>
<td>Fell from height of 4 m, landed on right arm</td>
<td>Strong winds, 20° C, dry</td>
</tr>
<tr>
<td>5</td>
<td>Thrown head first against a wooden pole on the beach</td>
<td>Stormy winds, 10° C, dry</td>
</tr>
</tbody>
</table>
DISCUSSION

To objectify the suspected high risk of serious injury associated with kitesurfing, this study described all kitesurfing-related injuries in the South West of the Netherlands, severe enough to warrant a HEMS dispatch in the past 3 years. Although popularity of the sport is on the rise, a search query in PubMed resulted in only two articles related to kitesurfing injuries. These studies described injury rates of 6 and 7 injuries per 1,000 kitesurfing hours, respectively. Although these rates are lower than that reported in other sports, like soccer or ice hockey, kitesurfing is a high-risk sport, because of the potential to cause severe injury. A recent prospective study by Nickel et al. described injury patterns related to kitesurfing. The most common injury location was found to be the foot/ankle (28%), followed by the knee and the chest. Serious injury was present in a small percentage of cases. The prevalence of fractures was 3%, and 0.8% of patients had multiple injuries. The present study shows a high percentage of fractures (three of five patients) and multiple severe injuries. However, this is explained by the fact that HEMS is only dispatched for seriously injured patients. The present study reported one fatality, as did Nickel et al. Fatal accidents during sports participation are considered rare. Recent reports have reported fatal accidents for skiing, American football, and windsurfing. Similar to injury mechanisms in other studies concerning kitesurfing, we found blunt impact trauma to be the mechanism most frequently involved in kitesurfing injuries. The athletes collided with stationary objects on shore. Three risk factors for collisions are proposed: surfing too close to shore, loss of kite control, and a specific wind condition, called onshore flow. When wind is directed toward a steep shore, possibly with obstacles like houses, the wind will be directed upwards after passing these obstacles. This may result in loss of control by the athlete as a result of the sudden lift. Loss of control combined with the inability to quickly release the kite from the harness is the primary cause of impact trauma. Finally, when a surfer is close to shore, the risk of collision after loss of control is bigger than when surfing in open sea. All of our patients did lose control as a result of one of these factors. One surfer even lost control before ever reaching the water.

Studies concerning injuries sustained during other related water sports are available. However, although common types of injuries sustained during windsurfing or wakeboarding and kitesurfing are similar, most serious injuries sustained by kitesurfers result from collision with objects, because kitesurfing is done close to shore. This is not the case in windsurfing or wakeboarding.

Another mechanism of injury encountered in kitesurfing is fall from height, i.e., vertical deceleration trauma. Injury patterns typically associated with such trauma are fractures of the spine and the lower limbs.

In an effort to improve safety and reduce concerns about the risks among policy makers, several groups have developed safety guides. A national organization for kitesurfing, the Dutch Kitesurfing Society, has put forward a list of safety measures, similar to international guidelines. Additionally, the introduction of a mandatory certificate of competence has been proposed. To date, no injury statistics concerning kitesurfing accidents are kept, nor can compliance to safety guidelines be determined. Overall incidence of injury cannot be determined without prospective study. Another explanation often given for accidents is inexperience of the surfer. However, experience does not exclude risk, since the only fatality regarded an instructor. Nevertheless, inexperience and fatigue are almost certainly main risk factors in the occurrence of accidents, but may not be an indicator for injury severity.

CONCLUSIONS

Kitesurfing is a relatively new “extreme” sport, which is currently depicted as being highly risky. In 3 years, Rotterdam’s HEMS was dispatched for five seriously injured kitesurfers. The main injuries were fractures, all resulting from collision of the surfer with an object. The reason for these collisions was a loss of control, most likely owing to wind conditions.

Without making any statements on the safety of the sport in general, the risk of sustaining serious, even life threatening injuries, is made apparent by reported cases. Knowledge and common sense should enable the surfer to increase his or her own safety, preferably combined with wearing safety gear, like helmets.

Physicians involved in treating victims of kitesurfing accidents should always consider the possibility of serious injury, resulting from high-energy trauma.

ACKNOWLEDGMENTS

We thank Gunnar Larsen, Watersports Scheveningen, and Henk Westbroek, of the Helicopter Mobile Medical Team, Lifeliner 2, Rotterdam for providing us with the photographs.

REFERENCES

Central Pulmonary Artery Embolism After Perihepatic Packing Because of Liver Trauma

Andreas Waltensdorfer, MD, Elisabeth Mahla, MD, Michael Zink, MD, Peter Oberwalder, MD, Hans-Joerg Mischinger, MD, and Helfried Metzler, MD

Severe trauma with liver rupture and uncontrolled bleeding is a serious, possibly lethal, event, necessitating early surgical intervention to control hemorrhage. Because definitive surgical treatment in most cases is not possible initially, perihepatic packing to control bleeding has gained widespread use in the last decades. Placing packs around the liver is meant to cause tamponade and therefore hemostasis. This procedure has also been successfully used in patients with HELLP (hemolytic anemia, elevated liver enzymes, low platelet count) syndrome or hepatocellular adenoma. Additional surgical intervention within the following days is necessary for unpacking and is definitive treatment. However, perihepatic packing itself may cause serious complications, such as hypotension and low cardiac output, abdominal compartment syndrome (ACS), and multiple organ failure because of ischemia of splanchnic and retroperitoneal organs, necessitating urgent decompression. A major complication of unpacking and decompression of the ACS is live-threatening bleeding. We describe a case of a fulminant pulmonary artery embolism (PAE) during urgent decompression of elevated intra-abdominal pressure (IAP) in a patient with perihepatic packing for rupture of the liver.

CASE REPORT

A 20-year-old woman sustained multiple injuries during a motor vehicle crash. She was intubated and ventilated at the location of the crash, because her initial Glasgow Coma Scale score was 3, and brought to our emergency department by helicopter. Computed tomography (CT) scan of the brain revealed a traumatic brain injury consisting of subarachnoid hemorrhage, a small intracerebral hematoma and mild brain edema. Furthermore, a fracture of an abnormal ankyloitic articulation of the atlanto-occipital joint with small epidural hematoma between C2 and C3 without dislocation were seen. The patient’s right humerus, the pelvis, and os sacrum were fractured. Ultrasonography of the abdomen showed free fluid and liver damage; a grade IV liver rupture was diagnosed (Fig. 1). During helicopter transport and the diagnostic procedure in our emergency department the patient’s circulation could be stabilized with 1,500 mL of colloids and 1,000 mL of colloid fluids. Immediate surgical exploration of the abdomen revealed vigorous bleeding from a liver laceration. The hemorrhage was controlled using sutures, fibrin glue, and perihepatic packing. Simultaneously, the right humerus was stabilized with a fixateur externe. A parenchymal pressure probe for intracranial pressure measuring was inserted.

Postoperatively, the patient was in a stable hemodynamic condition without signs of bleeding. The intracranial pressure never exceeded 10 cm of water. About 12 hours postoperatively, she gradually became hypotonic and tachycardic with decreased central venous pressure, and despite excessive volume substitution her conditions could not be stabilized (Table 1). There were no signs of bleeding from the liver laceration, and hemoglobin concentration remained stable despite a positive fluid balance. However, there were increasing clinical signs of elevated IAP, edema of the legs and the lower trunk with decreasing urine output, persisting low central venous pressure (Table 1) and tense abdominal wall. Cardiac tamponade was ruled out by echocardiography. After a short period of extreme bradycardia with circulatory arrest necessitating mechanical resuscitation, it was decided to re-explore the abdomen because of suspected ACS, perhaps because of intra-abdominal fluid or perihepatic packing. Re-opening the abdominal wall and unpacking the surgical pads led to initial increase of blood pressure, immediately followed by extreme hypotension, tachycardia, and finally, ventricular fibrillation.

After successful resuscitation, transesophageal echocardiography (TEE) showed hypokinesia of the interventricular septum with mild dilatation of the right ventricle. Furthermore, a rupture of the aortic wall was suspected. After smooth repacking and wound closure, a CT scan of the thorax
showed no signs of an aortic rupture, but bilateral central pulmonary artery embolism was found (Fig. 2). During these diagnostic procedures, multiple series of cardiac resuscitation were necessary. Emergent surgical intervention using cardiopulmonary bypass was performed. Large masses of thrombi were removed from both the right and left pulmonary artery. This procedure successfully led to full stabilization of the patient’s circulatory condition within several hours. The source of these thrombi was suspected to be the iliacal and femoral veins resulting from stasis because of compression of the IVC (inferior caval vein). Postoperatively there were no further signs of elevated IAP.

Four days later, after diagnostic exclusion of thrombi in the femoral and iliacal veins by phlebography and magnetic resonance tomography re-laparotomy for unpacking and definitive liver surgery was performed. During the next weeks, the young woman made an uneventful recovery without any neurologic deficit. There were no further episodes of right ventricular dysfunction and no pulmonary dysfunction occurred. There was no need for operative stabilization of her cervical or pelvic fractures. She was transferred to the general ward 31 days after her vehicle crash.

**DISCUSSION**

Our report describes the case of fulminant PAE after perihepatic packing in a patient with traumatic rupture of the liver. Perihepatic packing is a common surgical procedure to control hemorrhage in traumatic or spontaneous hepatic rupture. Besides the advantages of this procedure, several drawbacks exist, which must be monitored cautiously.

Perihepatic packing might lead to elevated IAP inducing signs of cardiopulmonary dysfunction. Meldrum et al., in a retrospective case series, impressively showed the amelioration of circulatory parameters, such as increased cardiac index, oxygen delivery, and decreased pulmonary capillary wedge pressure, immediately after removing perihepatic packing in patients with severe liver trauma. The same was found with respiratory parameters, such as decreased mean airway pressure and increased oxygenation index. Relieving elevated IAP may save patients in marginal cardiopulmonary condition.

Further elevation of IAP leads to ACS, an entity defined as elevated IAP greater than 20 to 25 mm Hg with concomitant organ dysfunction such as renal dysfunction or increasing airway pressure. Without recognition and urgent treatment of ACS, this situation will ultimately lead to multiple organ failure (MOF) and death. Liver trauma with perihepatic packing as emergency therapy can induce ACS, not only because of intra-abdominal organ edema and peritoneal fluid but also because of packing itself. Ertel et al. in a series of 311 patients with abdominal and/or pelvic trauma showed that 5.6% of the patients developed ACS, and in 47.1% of patients with ACS an abdominal packing had been performed. Urgent decompression in all cases is the therapy of choice.

Today, the gold standard for measuring IAP is measuring urinary bladder pressure via a pressure transducer. Yet in case of perihepatic packing, this method of measuring IAP might be questionable. Gadzijev et al., in their case series and in an additional animal study, showed that IAP measured by the pressure in the urinary bladder may not exactly reflect the pressure increase in the IVC in traumatized patients with perihepatic packing.

Within several hours postoperatively, our patient developed clinical signs of elevated IAP, showing persistent tachycardia and hypotension with concomitant low central venous pressure, despite resuscitation with crystalloid and colloid fluids, edema of the legs and the lower trunk, livid color, decreasing urine output and tense abdominal wall. During preparation for monitoring IAP, the hemodynamic condition rapidly deteriorated, necessitating urgent decompression. Peri-

**Table 1  Circulatory Parameters Related to Fluid Resuscitation in the First 20 Hours Postoperatively**

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>BP syst (mm Hg)</th>
<th>BP diast (mm Hg)</th>
<th>CVP (mm Hg)</th>
<th>HR (b/min)</th>
<th>Urine Output (mL/h)</th>
<th>Fluid Balance (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Hours</td>
<td>115</td>
<td>70</td>
<td>4</td>
<td>113</td>
<td>120</td>
<td>+530</td>
</tr>
<tr>
<td>10 Hours</td>
<td>90</td>
<td>55</td>
<td>4</td>
<td>124</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>12 Hours</td>
<td>75</td>
<td>50</td>
<td>4</td>
<td>115</td>
<td>40</td>
<td>+2430</td>
</tr>
<tr>
<td>15 Hours</td>
<td>65</td>
<td>45</td>
<td>2</td>
<td>104</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>20 Hours</td>
<td>80</td>
<td>45</td>
<td>3</td>
<td>138</td>
<td>40</td>
<td>+4970</td>
</tr>
</tbody>
</table>

BP syst, Systolic blood pressure; BP diast, diastolic blood pressure; CVP, central venous pressure; HR, heart rate.
haps in her case it would have been wiser to monitor the pressure of the IVC, which seems to more accurately represent pressure elevation because of perihepatic packing.10

Although a case of IVC thrombosis because of perihepatic packing is described by John at al.,11 to our knowledge a case of fulminant PAE in a patient with perihepatic packing after liver trauma has not been described yet. Perihepatic packing and ACS can each lead to compression of the IVC.10,12 We hypothesize that with compression of the IVC, blood flow in the dependent vessels (iliac and femoral veins) slowed down extremely leading to thrombosis,11 despite prophylactic heparinisation (fraxiparin 2500 IU/d). With sudden decompression, blood flow in these vessels immediately increased, disrupting the thrombi from the vessel wall. Those thrombi almost instantaneously obstructed a great portion of the central pulmonary artery, leading to circulatory collapse. The missing/failed diagnosis by TEE might have been the result of prolonged mechanical resuscitation pushing the emboli forward in the pulmonary artery and freeing parts of the lumen for restitution of blood flow, so that ultimately spontaneous circulation could be re-established.

To exclude perioperative hypercoagulation as a promoting factor for thrombosis, we monitored thrombelastography (TEG) (ROTEG, Pentapharm, Germany) and coagulation proteins. The modified heparinase TEG revealed increased reaction time and decreased maximal amplitude as signs of hypocoagulation, and the coagulation factors were within normal range or slightly decreased. Therefore, hypercoagulation did not seem to be a promoting factor for this thrombosis.

**CONCLUSION**

Perihepatic packing in patients with liver trauma may lead to ACS and to venous thrombosis of the lower part of the body. Obviously, decompression of ACS may not only increase the risk of rebleeding from severe liver trauma but also of pulmonary arterial embolism. If cardiocirculatory collapse occurs after decompression of perihepatic packing, PAE should be considered as a causative mechanism. Thus, circulatory collapse in these patients may not only originate from diminished preload because of ACS by perihepatic packing but also from increased afterload of the right heart, induced by massive pulmonary embolism.

**REFERENCES**


Thyroid Storm After Blunt Thyroid Injury: A Case Report

Akiyoshi Hagiwara, MD, Atsuo Murata, MD, Takeaki Matsuda, MD, Seiki Sakaki, MD, and Shuji Shimazaki, MD

Blunt direct thyroid injury is quite rare in trauma patients without preexisting goiter. Most of the reported cases have emphasized the need to closely monitor patients with thyroid injuries so that possible upper airway obstruction caused by an associated hematoma can be detected promptly. Previously, only one article reported thyrotoxicosis that resulted from increased serum thyroid hormone concentrations after direct thyroid injury. Thyrotoxicosis enhances the sympathetic nervous system activity that can lead to thyroid storm. To our knowledge, thyroid storm caused by increased serum thyroid hormone concentrations after direct thyroid gland injury has never been reported. We present here a case of a patient who developed abnormal thyroid secretion and thyroid storm symptoms after direct thyroid injury.

CASE REPORT

A healthy 20-year-old man with no previous medical history collided with a building at the roadside while riding a motorcycle. His mandible was crushed by the motorcycle handle bar. At admission, his Glasgow Coma Scale scores were eye (E) 4, verbal (V) 4, and motor (M) 6. Blood pressure (BP) was 120/85 mm Hg, and heart rate (HR) was 125 beats per minute. Injuries noted were contusion of the lower lip and mandible, a cervical hematoma in the region of the lower mandible, an open fracture involving the dorsum of the left middle finger, and swelling of the left lower leg. The patient was intubated after the primary survey, because massive bleeding from contusion of the lower lip was present in the mouth, and upper airway obstruction from cervical hematoma growth was a concern. Radiographs detected two fractures of the mandible, a mild left lung contusion, and fractures of the middle phalanx of the left middle finger and the left tibial shaft. No abnormalities were noted in computed tomography (CT) of the head. CT of the neck showed a subcutaneous hematoma overlying the lower mandible and a laceration of the right thyroid lobe surrounded by a hematoma (Fig. 1). Chest CT showed a mild lung contusion involving the left lower lobe. No abnormal findings were noted in the abdominal and pelvic CT. We cleaned and debrided the contusions, inserted a chest tube in the left pleural cavity, and performed open reduction and internal fixation of the open fracture of the middle phalanx of the left middle finger. Hemoglobin concentration was 8.6 g/dL on hospital day 1. After transfusion of 1 U each of packed red blood cells and fresh frozen plasma, hemoglobin concentration increased to more than 9 g/dL; no further transfusions were necessary.

Beginning on hospital day 2, an intermittent fever was present, with temperatures exceeding 39°C twice a day. The patient became confused. Coinciding with peaks of body temperature, systolic BP and HR significantly increased, from 90 to 160 mm Hg and 110 to 170 bpm, respectively.

In the predawn hours of day 4, hypotension (40/20 mm Hg) suddenly ensued, and the Glasgow Coma Scale scores fell to E 2, V (intubation), and M 4. A bolus infusion of 800 mL of crystalloid solution promptly increased BP to 120/35 mm Hg. A pulmonary artery catheter was then introduced to measure hemodynamic parameters. The cardiac index was 8.36 L · min⁻¹ · m⁻², whereas the systemic vascular resistance index was 680 dynes · s · m⁻² · cm⁻⁵, indicating a hyperdynamic state with high cardiac output and low systematic vascular resistance index (SVR) (Table 1). We initiated a continuous intravenous infusion of norepinephrine (0.02 μg · kg⁻¹ · min⁻¹) together with crystalloid solution at approximately 150 mL/h. BP then stabilized (systolic BP, 120–140 mm Hg; diastolic BP, 50–80 mm Hg), but tachycardia persisted (120–140 bpm). On day 5, HR gradually decreased, recovering to normal on day 6 (80–90 bpm). With complete stabilization of hemodynamics, norepinephrine was withdrawn on day 6. The patient then progressed uneventfully, undergoing internal fixation of mandibular fractures on day 35, using a plate. He was discharged home on day 62.

Results of thyroid tests from days 1 to 10 are shown in Table 2. Free thyroxine and free triiodothyronine concentrations on day 1 were high, 2.5 ng/dL (normal range,
0.83–1.77 ng/dL) and 6.3 pg/mL (normal range, 2.46–4.01 pg/mL), respectively. On day 3 both had increased to 4.0 ng/dL and 9.7 pg/mL, respectively; on day 4, when the patient developed shock, they were 3.1 ng/dL and 6.4 pg/mL, respectively. On day 7, they had decreased to 2.5 ng/dL and 4.6 pg/mL, respectively. On day 10, free thyroxine was slightly higher than normal (1.9 ng/dL), whereas free triiodothyronine had recovered to normal (3.5 pg/mL). Concentration of thyroid-stimulating hormone (TSH) had been consistently low from days 1 through 10 (Table 2). Measured on day 12, TSH receptor antibody was normal (4.7%; normal range, <10%).

### Table 1 Changes in Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Day</th>
<th>Heart rate (bpm)</th>
<th>Blood pressure (mm Hg)</th>
<th>Pulmonary arterial pressure (mm Hg)</th>
<th>Pulmonary capillary wedge pressure (mm Hg)</th>
<th>Systemic vascular resistance index (dynes · s · m⁻² · cm⁻⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>150</td>
<td>102/59</td>
<td>28/10</td>
<td>8</td>
<td>680</td>
</tr>
<tr>
<td>5</td>
<td>99</td>
<td>194/81</td>
<td>31/12</td>
<td>10</td>
<td>1,156</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>186/83</td>
<td>20/10</td>
<td>12</td>
<td>1,247</td>
</tr>
</tbody>
</table>

### Table 2 Changes in Thyroid Hormone Concentrations

<table>
<thead>
<tr>
<th>Day</th>
<th>FT4 (ng/dL)</th>
<th>FT3 (pg/mL)</th>
<th>TSH (μU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>6.3</td>
<td>0.47</td>
</tr>
<tr>
<td>2</td>
<td>4.1</td>
<td>8.6</td>
<td>0.19</td>
</tr>
<tr>
<td>3</td>
<td>4.0</td>
<td>9.7</td>
<td>&lt;0.03 &lt;0.03</td>
</tr>
<tr>
<td>4</td>
<td>3.1</td>
<td>6.4</td>
<td>&lt;0.03 &lt;0.03</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>4.6</td>
<td>0.24</td>
</tr>
<tr>
<td>6</td>
<td>1.9</td>
<td>3.5</td>
<td></td>
</tr>
</tbody>
</table>

FT4, free thyroxine (normal range, 0.83–1.77 ng/dL); FT3, free triiodothyronine (normal range, 2.46–4.01 pg/mL); TSH, thyroid-stimulating hormone (normal range: 0.50–5.00 μU/mL).

**DISCUSSION**

Blunt thyroid trauma is usually a result of a motor vehicle collision, occurring from hyperextension in a deceleration injury or from direct trauma. Reported cases of blunt thyroid injury have generally occurred in trauma patients with pre-existing goiter,8–11 because the injury is extremely rare in those without goiter.2–7

Our patient had no previous or present history of non-traumatic thyroid disease; serum TSH was low at admission to the hospital, whereas TSH receptor antibody was normal. These findings suggest that increased thyroid hormone concentrations resulted directly from traumatic rupture of thyroid follicles.

Laboratory analysis is usually not helpful in the diagnosis of thyroid storm, because thyroid function tests are not routinely available to emergency physicians. To identify thyroid storm caused by injury at an early stage, medical history, clinical symptoms, and routine laboratory tests would be necessary. Burch and Wartofsky12 assessed likelihood of thyroid storm using scores for seven clinical variables: body temperature, HR, central nervous system symptoms, gastrointestinal symptoms, congestive heart failure, atrial fibrillation, and jaundice. Total scores exceeding 45 were considered “highly suggestive” of thyroid storm. Accordingly, thyroid storm was very likely in our patient. From day 2, temperatures exceeding 39°C were recorded (20 points); central nervous system symptoms were present (confusion, 20 points); and tachycardia was prominent (110–170 bpm, 10–25 points; total points, 50–65).

Effects of thyroid hormones on the cardiovascular system include increased cardiac output and HR as well as vasodilation. These effects are particularly intense in thyroid storm, which is said to induce hyperdynamic shock.13 When our patient developed shock on day 4, hemodynamic evaluation showed a significant increase in cardiac index and a decrease in the systemic vascular resistance index. Moreover, hemodynamics improved when circulating thyroid hormone concentrations decreased. Shock in this patient, therefore, appears to have represented hyperdynamic shock caused by thyroid storm.

Treatment of thyroid storm can be classified into three major categories: (1) minimizing severe adrenergic symptoms using β-blockers, (2) decreasing excessive thyroid hormone synthesis using propylthiouracil or methimazole, and (3) decreasing the preformed thyroid hormone release using iodine. These three drugs are used in treatment of thyroid storm in patients with hyperthyroidism, and β-blocker is effective especially in controlling tachyarrhythmia. However, use of β-blocker in patients after profound shock, such as in our case, may be difficult. Now that we know the laboratory test results, in retrospect we could have used β-blocker on day 2, when our patient developed tachycardia. Because thyroid function tests are not routinely available to emergency physicians, possible thyroid storm should be considered and
treated, if tachycardia, a higher fever, and central nervous dysfunction develop in patients with blunt neck injuries involving thyroid rupture.

When clinical manifestations of hyperthyroidism persist and are followed by unexplainable hypotension, hemodynamic monitoring should be initiated using a pulmonary artery catheter. If a hyperdynamic state is demonstrated, thyroid storm may be responsible, requiring continued close clinical and hemodynamic monitoring.

REFERENCES