Preoperative Hematocrit Is a Powerful Predictor of Adverse Outcomes in Coronary Artery Bypass Graft Surgery: A Report From The Society of Thoracic Surgeons Adult Cardiac Surgery Database

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Background. Small series have identified a relationship between preoperative hematocrit (HCT) and outcomes in coronary artery bypass graft (CABG) surgery. The Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD) began collecting preoperative HCT data in 2008. In this study, analyses were performed to determine the impact of preoperative HCT on perioperative morbidity and mortality among patients undergoing isolated CABG.

Methods. Data were collected on 182,599 patients who underwent primary isolated on-pump CABG between 2008 and 2009 and were included in the STS ACSD. Data were included only from centers that performed more than 100 on-pump cases per year during the period of study. Dialysis patients as well as those with previous cardiovascular operations or missing data for HCT were excluded. We then performed multivariable analysis using the 2008 STS CABG risk model as a guide, including HCT as a predictor. Logistic regression was performed for operative mortality and other adverse outcomes.

Results. Overall operative mortality was 1.6% (3,005 of 182,599). Compared with patients with anemia (HCT <33%), patients with HCT of at least 42% had lower mortality (1.1% versus 3.4%; p < 0.0001) and lower rates of renal failure (2.0% versus 7.8%; p < 0.0001), stroke (0.9% versus 1.8%; p < 0.0001), prolonged ventilation (8.4% versus 17.5%; p < 0.0001), and deep sternal wound infection (0.3% versus 0.6%; p < 0.0001). In adjusted analyses, each 5-point decrease in preoperative HCT was associated with an 8% higher odds of death (odds ratio, 1.08; p < 0.0003), a 22% increase in the odds of postoperative renal failure (odds ratio, 1.22; p < 0.0001), and a 10% increase in the risk of deep sternal wound infection (odds ratio, 1.10; p < 0.01). Similar results were observed among patients (n = 74,292) undergoing elective CABG. The percentage of patients receiving perioperative blood transfusion decreased from 88.5% in the anemic group (HCT <33%) to 32.5% in patients with HCT of at least 42% (p < 0.0001).

Conclusions. Preoperative HCT is a powerful independent predictor of perioperative mortality as well as renal failure and deep sternal wound infection in patients undergoing isolated primary CABG operations. These findings should prompt investigation of strategies to increase preoperative HCT.


Previous small- and medium-sized observational studies have demonstrated an association between preoperative anemia and both fatal and nonfatal adverse outcomes after cardiac surgery [1–7]. Lower nadir hematocrits (HCTs) on cardiopulmonary bypass have also been associated with an increased risk of morbidity and mortality among patients undergoing cardiac operations, and the strongest predictor of lowest HCT on cardiopulmonary bypass is preoperative HCT [8–10]. Lower preoperative red blood cell mass, as reflected in lower HCT levels, increases the likelihood of perioperative allogeneic blood transfusion, which in turn [3] has a strong association with fatal and nonfatal adverse outcomes [11–14].

The Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD) began collecting information on preoperative HCT in 2008; therefore, preoperative HCT is not included in current STS risk models [15]. In this study, analyses were performed to determine the impact of preoperative HCT on perioperative morbidity and mortality among patients undergoing isolated coronary artery bypass graft (CABG) surgery.
Material and Methods

The Society of Thoracic Surgeons Adult Cardiac Surgery Database

The STS ACSD was established in 1989 to report surgical outcomes after cardiothoracic surgical procedures [16]. Patient data are entered from sites using uniform definitions (available online at http://www.sts.org) and certified software systems. Although participation in the STS database is voluntary, data completeness is high, with overall preoperative risk factors missing in fewer than 5% of submitted cases. The STS ACSD currently includes data from more than 90% of hospitals performing adult cardiac operations in the United States [17].

Because the data used in analyses of the STS ACSD represent a limited data set (no direct patient identifiers) that was originally collected for nonresearch purposes, and the investigators do not know the identity of individual patients, the analysis of these data was declared by the Duke University Health System Institutional Review Board to be research not involving human subjects and is therefore considered exempt (Duke University Health System Protocol 00005876) [18].

Beginning in 2008, the STS ACSD began collecting preoperative HCT. The present study population was derived from a population of patients undergoing CABG in STS ACSD-participating hospitals in 2008 and 2009. We excluded (1) patients who underwent CABG without cardiopulmonary bypass, (2) patients who underwent operation at centers that performed fewer than 100 CABG operations in each year, (3) patients who were on dialysis preoperatively, (4) patients who had previous cardiac operations, and (5) patients with missing information on sex, age, or HCT. The final analysis population consisted of 182,599 patients.

Statistical Analyses

Demographics, preoperative risk factors, and outcomes were summarized. Distribution of preoperative HCT and its association with observed mortality, as well as the association with transfusion, were depicted graphically. Univariate associations between outcomes and HCT groups (anemia, <33%; and normal, ≥42%) were tested using χ² tests. Multivariable logistic analyses were performed for the following outcomes: operative mortality (defined as in-hospital death or death within 30 days of surgery), permanent stroke, postoperative myocardial infarction, renal failure (defined as an increase of serum creatinine to >2.0 mg/dL with an increase of at least twice the most recent preoperative creatinine level or a new requirement for dialysis postoperatively), deep sternal wound infection, and prolonged ventilation greater than 24 hours and postoperative length of stay greater than 14 days. The method of generalized estimating equations (GEE) was used for estimating model coefficients and standard errors. The list of all candidate predictors of STS 2008 CABG risk models was used as the starting point, and preoperative HCT was included as a predictor. Additional sets of multivariable logistic regression models were fitted on selected subpopulations, including patients who did not receive transfusion as well as patients who underwent elective surgery, defined as surgery on a patient whose cardiac function has been stable in the days or weeks before the operation and for whom the procedure could be deferred without increased risk of compromised cardiac outcome. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

Results

We identified 182,599 patients who underwent primary isolated on-pump CABG between January 2008 and December 2009. Patient characteristics are outlined in Table 1. The median age was 65 years, 27% were women, and the mean ejection fraction was 0.513. The median preoperative HCT was 39% (interquartile range, 36% to 42%). The distribution of preoperative HCT is illustrated in Fig 1. The preoperative HCT was less than or equal to 36% in 30.1% (54,948 of 182,599) of patients and was less than 39% in 43.8% (79,982 of 182,599) of the population. Overall operative mortality was 1.6% (3,005 of 182,599), and selected outcomes are presented in Table 2. Although not a focus of this manuscript, the excellent overall outcomes for this population of patients should be noted.

In univariate analysis, the preoperative HCT was strongly predictive of operative mortality (Fig 2). Mortality declined from 3.4% among patients with a preoperative HCT of less than 33% to 1.1% among patients with a HCT of at least 42%. In additional univariate analyses, a preoperative HCT less than 33% compared with at least 42% was associated with lower rates of renal failure (2.0% versus 7.8%; p < 0.0001; Fig 2), stroke (0.9% versus 1.8%; p < 0.0001), prolonged ventilation (8.4% versus 17.5%; p < 0.0001), and deep sternal wound infection (0.3% versus 0.6%; p < 0.0001). There was a clear effect for mortality and all major morbidities, with the lowest frequencies of death or complications observed with preoperative HCT levels of at least 42%.

In multivariable analyses, each 5-point decrease in preoperative HCT was associated with an 8% higher odds of death (odds ratio, 1.08; p < 0.0001), a 22% increase in the risk of deep sternal wound infection, and a 10% increase in the risk of prolonged ventilation greater than 14 days. The method of generalized estimating equations (GEE) was used for estimating model coefficients and standard errors. The list of all candidate predictors of STS 2008 CABG risk models was used as the starting point, and preoperative HCT was included as a predictor. Additional sets of multivariable logistic regression models were fitted on selected subpopulations, including patients who did not receive transfusion as well as patients who underwent elective surgery, defined as surgery on a patient whose cardiac function has been stable in the days or weeks before the operation and for whom the procedure could be deferred without increased risk of compromised cardiac outcome. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC).
wound infection (odds ratio, 1.10; \( p < 0.01 \); Table 3). Similar results were observed among the subpopulation of patients (n = 74,292) undergoing elective CABG (Table 4).

Table 5 summarizes the estimated associations between preoperative HCT and the outcomes in the other subpopulation of patients who did not receive transfusion (n = 83,235). Although the odds ratio for operative mortality was similar in this analysis compared with the previous regression that included the entire population of patients, the probability value was not significant. It should be noted though that there were only 398 deaths among this population of 83,235 patients and low event rates typically reduce the power of statistical tests. The significant association with renal failure remained in this population.

Figure 3 demonstrates the relationship between preoperative HCT and the likelihood of needing any packed red blood cell transfusion perioperatively. There was a decrease in the percentage of patients receiving perioperative blood transfusions from 88% in the anemic group (HCT <33%) to 33% in patients with HCT of at least 42% (\( p < 0.0001 \)).

Comment

The key findings of this study include the following: (1) among a contemporary national experience of more than 180,000 patients undergoing primary isolated CABG, the preoperative HCT is a powerful independent predictor of mortality, renal failure, deep sternal wound infection, and prolonged hospital stay; (2) of all the morbidity and mortality outcomes examined in this study, the preoperative HCT has the greatest and most consistent impact on the risk of renal failure; (3) similar outcomes were observed in the subpopulation of elective patients; (4) for all major morbidities and mortality, there was a nadir consistently observed between HCT values of 42% and 46%; and (5) the likelihood of perioperative transfusion was dramatically influenced by the preoperative HCT.

The current STS risk models for CABG do not include preoperative HCT [15] because this data element was only added to the STS ACSD in 2008 with data collection version 2.6.1. The present findings support adding preoperative HCT to future risk models. The great importance of the preoperative HCT as a predictor of outcomes is that it is one of only a few potentially modifiable risk factors, and the results of this study support further investigation of strategies to optimize preoperative HCT before cardiac operations.

Others have also identified preoperative HCT as a predictor of outcomes in smaller studies. Ranucci and colleagues [19] examined 3,003 consecutive CABG patients who did not receive perioperative transfusions and found that preoperative HCT predicted morbidity but not

**Table 2. Early Outcomes (n = 182,599)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative mortality</td>
<td>1.7%</td>
</tr>
<tr>
<td>Permanent stroke</td>
<td>1.2%</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3.5%</td>
</tr>
<tr>
<td>Deep sternal wound infection</td>
<td>0.4%</td>
</tr>
<tr>
<td>Prolonged ventilation</td>
<td>10%</td>
</tr>
<tr>
<td>Postoperative LOS &gt;14 d</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

LOS = length of stay.
mortality. In a later study of 13,843 patients undergoing all types of cardiac operations, these authors created propensity-matched groups of 401 anemic (mean HCT, 27%) and nonanemic (mean HCT, 39%) patients and found the anemic group to have significantly higher rates of morbidity (27% versus 17%) and mortality (12.7% versus 7.5%) [20]. The impact of preoperative HCT levels on the risk of postoperative renal failure has been reported by DeSanto and colleagues [21], who reported that among 1,047 patients undergoing CABG, preoperative anemia independently predicted postoperative acute kidney

Table 3. Multivariable Regression Model With Outcome of Preoperative Hematocrit Decreasing 5%, All Patients (n = 182,599)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital/30-d mortality</td>
<td>1.08 (1.04–1.13)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Permanent stroke</td>
<td>0.98 (0.94–1.03)</td>
<td>0.4409</td>
</tr>
<tr>
<td>Renal failure (newly developed)</td>
<td>1.22 (1.19–1.25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postoperative LOS &gt;14 d</td>
<td>1.10 (1.08–1.13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Deep sternal infection</td>
<td>1.10 (1.03–1.19)</td>
<td>0.0074</td>
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</tbody>
</table>

CI = confidence interval; LOS = length of stay; OR = odds ratio.

Table 4. Elective Patients With Outcome of Preoperative Hematocrit Decreasing 5% (n = 74,292)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital/30-d mortality</td>
<td>1.12 (1.04–1.22)</td>
<td>0.0049</td>
</tr>
<tr>
<td>Permanent stroke</td>
<td>0.99 (0.91–1.08)</td>
<td>0.8953</td>
</tr>
<tr>
<td>Renal failure (newly developed)</td>
<td>1.29 (1.23–1.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postoperative LOS &gt;14 d</td>
<td>1.09 (1.04–1.14)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CI = confidence interval; LOS = length of stay; OR = odds ratio.
injury. Our findings confirm and extend these observations in a very large contemporary series representing more than 90% of centers performing cardiac surgery in North America.

We found that the risk of death after CABG increased by 8%, and the risk of renal failure by 22%, with every 5-point drop in preoperative HCT. The biologic mechanism for this relationship is likely multifactorial. We have demonstrated a clear-cut relationship between preoperative anemia and the likelihood of requiring a perioperative blood transfusion. Blood transfusion is associated with risks of infection, transfusion-associated lung injury, complex immunologic effects, graft-versus-host disease, and the potential for transfusion service errors. The effects of anemia are inextricably tied to the effects of transfusion, and it is impossible to completely separate the two in any observational study. It is plausible that some of the risk associated with preoperative anemia is attributable to transfusion. To this end, most cardiac surgery programs have adopted a blood conservation strategy in an effort to avoid transfusion. It is likely, though, that other mechanisms are involved as well. In our study, we demonstrated a significant relationship between postoperative renal failure and preoperative anemia even in patients who did not receive transfusion. Anemia decreases oxygen delivery to tissues, and end-organ dysfunction can ensue, particularly in patients with atherosclerotic disease. A key component of all blood conservation programs is the tolerance of lower hemoglobin concentrations, but no clearly safe lower limit has been defined as of yet [10, 22].

It is tantalizing to consider the potential impact of strategies to improve preoperative HCT before cardiac operation as a means of improving outcomes. In this investigation we have identified a dose-response relationship between preoperative HCT and both morbidity and mortality, with an optimal target preoperative HCT of between 42% and 46%. A pharmaceutical intervention that had the effect of moving the preoperative HCT into this optimal target range could potentially improve outcomes for a large number of patients. The most promising approach would likely include administration of an erythropoiesis-stimulating agent and iron before operation to a subpopulation of anemic patients. In one small retrospective series, Cladellas and associates [23] reported that the preoperative administration of erythropoietin (EPO) and iron to cardiac surgical patients resulted in a significant and important decrease in morbidity and mortality and a decrease in the percentage of patients receiving transfusion. Yoo and coworkers [24] randomly assigned 74 patients with anemia to receive EPO and iron 1 day before operation and observed a significant decrease in the percentage requiring transfusion. In contrast, D’Ambra and colleagues [25] performed a prospective randomized trial of 187 CABG patients in which the study group received EPO and iron starting 5 days before operation and did not observe an effect on transfusion or clinical outcomes. This trial was performed in a predominantly male population with few patients having preoperative anemia. Song and associates [26] performed a pilot study that included 71 elective CABG patients randomly assigned to EPO or control given intravenously on induction of anesthesia. This group reported a significantly

Table 5. Multivariable Regression Model With Outcome of Preoperative Hematocrit Decreasing 5%, Patients Without Transfusion (n = 83,235)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital/30-d mortality</td>
<td>1.07 (0.94–1.23)</td>
<td>0.3013</td>
</tr>
<tr>
<td>Permanent stroke</td>
<td>1.01 (0.90–1.13)</td>
<td>0.8622</td>
</tr>
<tr>
<td>Renal failure (newly developed)</td>
<td>1.11 (1.03–1.20)</td>
<td>0.0066</td>
</tr>
<tr>
<td>Postoperative LOS &gt;14 d</td>
<td>0.94 (0.86–1.04)</td>
<td>0.2316</td>
</tr>
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CI = confidence interval; LOS = length of stay; OR = odds ratio.

Fig 3. Perioperative red blood cell (RBC) transfusion rate by preoperative hematocrit.
lower rate of acute kidney injury in the EPO-treated group, with no difference in perioperative HCTs, suggesting a nonhematologic impact of EPO on renal function. Finally, a meta-analysis that reviewed a total of 708 patients who underwent cardiac surgery from 11 different studies concluded that perioperative EPO use was effective in lowering the need for transfusion [27]. Using EPO and iron in this way would be off-label, and larger studies that address effectiveness and safety are required before any official recommendations could be issued. Given the impact of anemia on risk that we and others have now shown, perhaps a larger trial is now justified in anemic patients scheduled for elective cardiac surgery.

Anemia may be a proxy for other systemic disease that increases risk not explained by other currently measured preoperative variables. Certainly, renal function cannot be completely measured by a single preoperative creatinine level, and the addition of preoperative HCT may simply provide a more accurate measure of renal function. Additionally, anemia may be a marker for poor nutrition and frailty. It is therefore possible that anemia is a correlate rather than a cause of poorer outcomes after CABG; investigations that measure the effect of moving HCT upward before surgery could answer this question. Weaknesses of this study include the retrospective nature of any analysis of the STS ACSD as well as the difficulty in separating the effects of anemia and transfusion. Only short-term outcomes are available in the STS ACSD, and any impact on long-term outcomes cannot be investigated.

In summary, preoperative anemia is an important predictor of morbidity and mortality after isolated primary CABG. Anemia has the largest effect on the development of postoperative renal failure. Preoperative HCT levels have a dose-response relationship with both mortality and morbidity, and it appears that the optimal preoperative HCT is between 42% and 46%. Hematocrit is not currently part of the STS risk models, and consideration should be given for inclusion in the future to improve accuracy. Interventions to raise HCT in elective cardiac surgical patients should be investigated.

References
DISCUSSION

DR NIV AD (Falls Church, VA): It is an excellent presentation and a very timely, appropriate topic. I was a little surprised about the effect of transfusion. When you took the patients that were not transfused, it altered the significance of preoperative hematocrit. We know that basically the indications for transfusion across the US and maybe worldwide are so variable. So I wonder what you all think about this specific finding of transfusion alteration on the significance of hematocrit?

DR WILLIAMS: To rephrase your question, at what point should we transfuse patients with a low hematocrit?

DR AD: Well, you showed that if you take out patients that were transfused, you demonstrated that actually preoperative hematocrit is nonsignificant, or the other way around. So why do you think that is?

DR WILLIAMS: Well, I guess I would argue with the premise of the question, respectfully, Dr Ad. The operative mortality odds ratio is essentially the same, and you are dealing with an event rate that is extremely low, death; there were fewer than 400 deaths. And so the power of the analysis to detect a statistically significant effect is weak. There was a statistically significant effect on renal failure that showed that there was a correlation between lower hematocrit and increasing rates of renal failure.

So I think that the fundamental question is, why is preoperative hematocrit a predictor? What is the biologic mechanism? Is it the transfusion is bad and those patients are more likely to get transfusion or is it that it’s a proxy for other systemic disease that is not captured by other predictors? And I think that is an unknown right now.

DR HOWARD SONG (Portland, OR): It seems like your stronger signal was in renal failure, so can we talk about renal failure for a second? Based on your finding that preoperative anemia is associated with perioperative renal failure, would you advocate transfusing a patient who is presenting for surgery and is anemic to avoid or reduce the chance that the patient would develop renal failure perioperatively?

DR WILLIAMS: I would not. It hinges on any setting, including in cardiac surgery, transfusion has been correlated with poor outcomes, and I don’t think that one can advocate for that. The other question is, should we do something to raise the hematocrit among patients where we have the luxury of time?

DR AD: Well, I agree with everything you said. I think it’s a fundamental problem that we can’t really have a specific answer, we can only speculate, because we know the limitation of the STS database, especially with this specific topic. So we are challenged to save transfusion and reduce preoperative risk by addressing different mechanisms to treat patients with low hematocrit that I believe, more than anything, is a surrogate of a sicker patient, and it is very hard to separate this from other factors. So I think we need to maybe, through CTSNet, go forward with some prospective randomized studies of mode of treatment to eliminate this risk.