The Risk of Acute Kidney Injury With Co-Occurrence of Anemia and Hypotension During Cardiopulmonary Bypass Relative to Anemia Alone

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Background. Postoperative acute kidney injury (AKI) is a common serious consequence of cardiac surgery. One recent study found higher AKI rates when anemia and hypotension occurred during cardiopulmonary bypass (CPB) relative to anemia alone. To revalidate this post hoc observation we analyzed detailed data from a large cardiac surgery cohort.

Methods. Patient, procedural, and outcome data were collected for nonemergent aortocoronary bypass and valve surgeries between July 2001 and September 2012. The occurrence of AKI (as defined by the Acute Kidney Injury Network criteria) was analyzed relative to known renal risk factors, and CPB hematocrit and blood pressure determinations in univariate and multivariable linear regression analyses.

Results. In our 3,963-patient cohort, we did not observe different AKI rates with the co-occurrence of anemia and hypotension relative to anemia alone (41.6% versus 44.3%; p = 0.39). Secondary analyses using linear definitions for AKI, CPB anemia, and hypotensive burden, and assessing for coincident timing also did not demonstrate significant association of anemia and hypotension with AKI risk relative to anemia alone.

Conclusions. In a large cohort of cardiac surgery patients, we did not confirm any association of cardiac surgery–related AKI risk with the co-occurrence of hypotension and anemia during CPB relative to anemia alone. More detailed analyses also failed to support an anemia-hypotension interaction. Additional studies are required to better understand the relationship among anemia, hypotension during CPB, and postoperative AKI, but existing evidence is insufficient to support changes in clinical practice.

Acute kidney injury (AKI) is a common serious complication of cardiac surgery associated with postoperative morbidity, mortality, and increased cost. As many as 30% of patients undergoing nonemergent cardiac surgery procedures sustain AKI, with 1% to 2% requiring renal replacement therapy [1-3]. Even modest AKI episodes are linked to adverse outcome [4], and patients requiring new-onset postoperative dialysis have mortality rates exceeding 60% [5]. Many perioperative AKI risk factors relate to variables that may reduce oxygen delivery to tissues, such as anemia and hypoperfusion [1].

Prevention remains the primary strategy to combat AKI. Given the kidney’s vulnerability to ischemia/reperfusion injury, factors amenable to treatment such as anemia and hypotension during cardiopulmonary bypass (CPB) have therefore gained attention [6, 7]. We and others have previously reported an association of low hematocrit values (eg, less than 21% to 24%) during CPB with increased AKI risk [8-10]. Notably, low blood pressure during CPB (eg, less than 50 mm Hg with preserved perfusion rates) has not been associated with changes in AKI risk in several studies [8, 11-13]. However, a recent study noted increased AKI risk when CPB anemia and hypotension occurred, compared with anemia alone [13]. The researchers highlighted the secondary post hoc nature of their observation, and the importance that it be validated in another patient population. Therefore, we tested the hypothesis that AKI risk is increased when anemia and hypotension occur during CPB relative to anemia alone.

Patients and Methods

Patient Selection

With Institutional Review Board approval, a study sample was identified from the population of consecutive adult patients undergoing on-pump nonemergent (aortocoronary bypass graft) CABG and valve surgery at a single institution between July 2001 and September 2012 (Fig 1). Excluded were patients with end-stage renal disease,
preoperative need for inotropes, and redo or emergent procedures. Additional postprocedure exclusion criteria included patients requiring renal replacement therapy or death within the first 2 days, because in these circumstances serum creatinine values do not accurately reflect the degree of AKI. Patient and procedural data collected included previously known renal risk factors (Table 1) [1, 3]; these were obtained from the Duke Databank for Cardiovascular Diseases. The databank is prospectively compiled during the hospital stay from contemporaneous medical records, custom data sheets, and laboratory results; quality assurance includes subsequent random chart review for completeness. Survival data was provided by the Duke Clinical Research Institute Follow-Up Group [14]. Data pertaining to CPB were obtained from automated anesthesia records (Innovian Anesthesia; Dräger Medical, Telford, PA). Information pertaining to the postoperative course were from the prospectively gathered Duke Quality Measurement and Management Initiative database.

Renal Function Assessment
Preoperative creatinine and daily postoperative serum creatinine values were measured until hospital discharge as per institutional protocol. Serum creatinine was measured using the Jaffe technique (UniCel DxC 800; Beckman Coulter, Brea, CA) with a normal range of 31 to 76 μmol/L (0.4 to 1.0 mg/dL) for females and 46 to 99 μmol/L (0.6 to 1.3 mg/dL) for males. Preoperative serum creatinine was obtained within 1 week before surgery, and defined as the value recorded closest to but not on the day of surgery. The peak postoperative creatinine (Cr\text{max,Post}) value was the highest of the daily in-hospital postoperative creatinine values. The primary outcome of AKI was characterized using Acute Kidney Injury Network criteria [15] modified to reflect the absence of urine output data (postoperative serum creatinine rise greater than 50% or 0.3 mg/dL within a 48-hour period), as in the study by Haase and colleagues [13]. Linear characterizations of AKI were also generated, using the preoperative to peak postoperative change in serum creatinine expressed as an absolute value (ΔCr) or as a percentage of Cr\text{Pre} (%ΔCr).

Anemia and Hypotension
During CPB, hematocrit was assessed every 30 minutes (GEM Premier 3000 and IL 682 CO-Oximeter; Instrumentation Laboratories, Bedford, MA). Mean arterial blood pressure was recorded automatically every 30 seconds; values below 20 mm Hg or above 299 mm Hg were considered erroneous and excluded from analysis. A previously reported index of CPB hypotension, log\text{TM50} [10] that was also employed for this purpose in the paper by Haase and colleagues, was then calculated for each patient to quantify a burden of hypotension during CPB. Log\text{TM50} is the log of the degree-duration integral of mean CPB blood pressures below 50 mm Hg multiplied by the duration in minutes. For example, a 10-minute episode during which the blood pressure was 30 mm Hg would be reflected by a TM50 of 200 min \cdot mm Hg, as calculated by the following: 10 min \times (50 – 30 mm Hg) = 200 min \cdot mm Hg. Likewise, a 60-minute episode at 40 mm Hg would accumulate a TM50 of 600 min \cdot mm Hg.

Anesthesia and Surgery
Anesthesia was managed per the attending anesthesiologist’s preference. Use of agents with potential renal effects (eg, intravenous dopamine, antifibrinolytic agents) was not regulated. Although availability of the various antifibrinolytic agents (eg, aprotinin) changed during the study period, administration of ε-aminocaproic acid was typical for elective nonemergent coronary artery bypass graft surgery and valve procedures such as those in the sample population throughout the study period [10].

The CPB circuit was primed with mannitol (50 g 25% solution), sodium bicarbonate (50 mEq 8.4% solution), heparin (10,000 units), albumin (50 mg 25% solution), crystalloid solution (Normosol; Hospira, Lake Forest, IL), and packed red blood cells if necessary to achieve a hematocrit no lower than 0.20 during CPB. Extracorporeal
perfusion was maintained using a nonpulsatile flow of 2 to 2.4 L/min \( \times \cdot \text{C}^{-1} \cdot \text{m}^{-2} \). The Terumo Capiox (Terumo Cardiovascular Systems, Ann Arbor, MI) hollow fiber membrane oxygenator with integrated arterial filter was used in most cases. The arterial carbon dioxide tension was maintained throughout CPB at 35 to 40 mm Hg (uncorrected for temperature), with the arterial oxygen tension maintained at 150 to 250 mm Hg. Target mean arterial pressure was between 50 mm Hg and 70 mm Hg during CPB with use of intravenous phenylephrine or sodium nitroprusside as required. Blood cardioplegia delivered between 6°C and 8°C was the myocardial protection strategy of choice. Target inflow temperature during CPB was 32°C, and patients were actively re-warmed to a nasopharyngeal temperature of 36.5°C before discontinuation of CPB. Except during heparin anticoagulation, shed blood was not reinfused. Postoperative mediastinal shed blood was discarded. Intraoperative cell salvage was used in most cases in which a cell-saving device was used, and all salvaged blood was washed before reinfusion. The average crystalloid fluids administered in the first 24 hours postoperatively was 1,000 mL to 1,500 mL of lactated Ringer’s solution and 500 to 1,000 mL of a colloid solution.

### Statistical Analysis

Univariate comparisons including patient and procedural characteristics, and renal function data were made using Student’s \( t \) tests for continuous variables and \( \chi^2 \) or Fisher’s exact tests for categorical variables.

To assess the post hoc finding of Haase and colleagues [13] linking the co-occurrence of CPB anemia and hypotension with increased AKI risk relative to anemia alone was the goal of our primary analysis. Haase and colleagues [13] reported a higher incidence of AKI in patients with both anemia and hypotension compared to patients with anemia alone.
colleagues [13] defined “hypotension during CPB” for subjects sustaining hypotension whose cumulative TM50 burden was in the highest 25% of the study population. In contrast, subjects who sustained anemia during CPB were those whose minimum hematocrit during CPB was in the lowest 25%. We used these characteristics to generate samples for univariate comparison of AKI rates (using modified Acute Kidney Injury Network criteria) in patients who sustained anemia and hypotension during CPB, and anemia (alone) during CPB.

Secondary linear regression analyses to identify factors associated with AKI (\(\%\Delta Cr\)) were performed using continuous characterizations of the predictors of interest. Therefore, instead of dichotomous definitions for CPB anemia (ie, lowest CPB hematocrit) and hypotension (ie, TM50), we used lowest CPB hematocrit and TM50 in place of hypotension as linear variables for inclusion in multivariable linear analyses. The same covariates were used as in the primary analysis. Also, to assess for any relationship with AKI of concurrent timing of hypotension and anemia, another secondary analysis was performed. For each patient the median of five blood pressure measurements closest to the time-stamped lowest CPB hematocrit determination was used in a multivariable model to assess for AKI risk (\(\%\Delta Cr\)). An interaction term (blood pressure\textsuperscript{lowest hematocrit} was included in this analysis and tested for association with AKI. The model was adjusted for the same covariates.

A \(p\) value less than 0.05 was considered significant. All statistical analyses were performed using the SAS statistical software version 8.0 (SAS Institute, Cary, NC).

**Results**

Patient, procedural, and renal function data are presented in Tables 1 and 2. The final analysis sample included 3,963 patients, after exclusion for preoperative inotrope use, death less than 2 days after surgery, preoperative dialysis, and postoperative dialysis (Fig 1). Acute kidney injury was common, occurring in 36.3% of patients, and the incidence of new-onset postoperative dialysis was 1.11% (\(n = 44\)). Four patient groupings were created based on before-study definitions of CPB anemia and hypotension as outlined above, and included patients with (1) CPB anemia and CPB hypotension (lowHCT/lowBP; \(n = 409\)); (2) CPB anemia alone (lowHCT only; \(n = 573\)); (3) CPB hypotension alone (lowBP only; \(n = 922\)); and (4) neither CPB hypotension nor CPB anemia (nmlHCT/nmlBP; \(n = 2,059\)).

In our primary analysis, we did not confirm a difference in AKI rates between the lowHCT/lowBP and lowHCT only groups (41.6% versus 44.3%; \(p = 0.39\); Fig 2). A similar analysis including all patients who died within 48 hours of surgery or required new-onset dialysis (Fig 1) also found no association of hypotension and the risk of AKI with anemia (\(p = 0.29\)). Other comparisons demonstrated strong associations between CPB anemia and postoperative AKI, including lowHCT/lowBP versus lowBP only groups (41.6% versus 35.4%; \(p = 0.03\), and lowHCT/lowBP versus nmlHCT/nmlBP groups (41.6% versus 33.4%; \(p = 0.0002\)). Additionally, patients in the lowHCT only group had a greater AKI risk than either the lowBP only group (44.3% versus 35.4%; \(p = 0.0005\) and the nmlHCT/nmlBP group (44.3% versus 33.4%; \(p < 0.0001\)). Finally, our findings did not demonstrate an association of CPB hypotension with AKI: lowBP only versus nmlHCT/nmlBP groups, 35.4% versus 33.4% (\(p = 0.29\)).

Our secondary analyses that used continuous variables to reflect lowest CPB hematocrit, hypotension burden, and AKI, also adjusting for previously known renal risk factors, did not identify any interaction between CPB hypotension and anemia as predictors of AKI risk (Table 3); the interaction term tested in this model was nonsignificant (\(p = 0.68\)). Finally, in our assessment to explore the relationship of concurrent hypotension with anemia-related AKI risk while accounting for standard AKI risk factors, the interaction term was also insignificant (\(p = 0.24\); Table 4, Fig 3).

**Comment**

Our study findings contrast with those of Haase and colleagues [13] in that we could not confirm any association of cardiac surgery–related AKI risk with the

<p>| Table 2. Renal Function Descriptors |</p>
<table>
<thead>
<tr>
<th>Renal Function Descriptor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak postoperative serum creatinine, mg/dL</td>
<td>1.5 (0.96)</td>
</tr>
<tr>
<td>Rise in serum creatinine, mg/dL</td>
<td>0.35 (0.68)</td>
</tr>
<tr>
<td>Postoperative serum creatinine rise ≥1.0 mg/dL</td>
<td>8.2</td>
</tr>
<tr>
<td>Postoperative serum creatinine rise ≥2.0 mg/dL</td>
<td>2.7</td>
</tr>
<tr>
<td>Postoperative serum creatinine rise 50% to 100% (RIFLE stage R)</td>
<td>18.0</td>
</tr>
<tr>
<td>Postoperative serum creatinine rise &gt;100% to 200% (RIFLE stage I)</td>
<td>6.4</td>
</tr>
<tr>
<td>Postoperative serum creatinine rise &gt;200% (RIFLE stage F)</td>
<td>2.0</td>
</tr>
</tbody>
</table>

\(\text{RIFLE} = \text{risk, injury, failure, loss, end-stage renal disease.}\)
The co-occurrence of hypotension and anemia during cardiopulmonary bypass (CPB) do not differ statistically from those of anemia alone, but do differ from patients with hypotension alone and patients with neither anemia or hypotension.

In a primary assessment designed to replicate the original observations of the Haase group in 920 patients, we observed no significant risk of AKI associated with CPB anemia and hypotension relative to anemia alone ($p = 0.39$), despite our greater sample size ($n = 3,963$). In a secondary analysis using continuous variables designed to allow for expression of more subtle effects, we also could not confirm any association of AKI with CPB anemia and hypotension compared with anemia alone ($p = 0.68$). Finally, in an analysis designed to assess concurrent CPB hypotension and anemia relative to anemia alone, we also found no association with AKI ($p = 0.24$). We did, however, note strong associations of CPB anemia with AKI risk in all of the above analyses, as has been previously reported. Also in these analyses, we found no association between CPB hypotension (alone) and postoperative AKI.

As acknowledged above, our study is not the first to ask whether the risk of AKI after cardiac surgery associated with CPB anemia changes when hypotension also occurs. In fact, in their 2012 publication Haase and colleagues [13] observed such an effect in a post hoc analysis, which they emphasized required validation in a second population. These investigators observed a 3.36-fold increase in the AKI rate ($p = 0.01$) with CPB anemia and hypotension compared with patients who had anemia alone. Despite our large sample size, equivalent case complexity, and detailed data, we could not demonstrate a similar finding. Rather than confirming the previous study findings, our analyses lend support to the possibility, as acknowledged by Haase and colleagues [13], that their post hoc analysis is a spurious finding. The importance of CPB anemia as a

### Table 3. Linear Multivariable Acute Kidney Injury Risk Factor Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum hematocrit during CPB</td>
<td>-0.84</td>
<td>0.0079</td>
</tr>
<tr>
<td>Log TM50</td>
<td>0.52</td>
<td>0.41</td>
</tr>
<tr>
<td>Female</td>
<td>0.78</td>
<td>0.74</td>
</tr>
<tr>
<td>White race</td>
<td>-7.53</td>
<td>0.0017</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>0.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>0.78</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7.45</td>
<td>0.0010</td>
</tr>
<tr>
<td>Baseline serum creatinine, mg/dL</td>
<td>-6.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Valve procedure</td>
<td>-7.44</td>
<td>0.0034</td>
</tr>
<tr>
<td>CPB duration, min</td>
<td>0.20</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CPB = cardiopulmonary bypass; TM50 = time-pressure integral mean CPB blood pressure less than 50 mm Hg.
predictor of postoperative AKI is well established, less so the significance of hypotension (with CPB flow preserved) [8, 10-13, 16-18]. Nonetheless, findings such as those by Ono and colleagues [19] that AKI risk is associated with CPB blood pressure benchmarked to reflect hypotension excursions relative to a patient’s own cerebral autoregulatory threshold highlight the incomplete understanding of this issue, and the need for more research to assess optimal blood pressure management during CPB.

We recognize our study has limitations, many of which are inherent to its retrospective design, including the possibility of missing risk factors that could contribute to confounding bias. In addition, our primary findings describe associations rather than causation; hence, although interventions such as transfusion and vasoactive agent administration would correct anemia or hypotension, that should not lead to an assumption that these therapies would necessarily prevent AKI. Additionally, it is important to recognize that owing to lack of data, we could not explore the importance of pump flow rates during CPB, and thus any potential implications it may have on oxygen delivery. However, we believe that including pump flow in any future analyses would be an interesting potential area for further study. Nonetheless, in the absence of randomized controlled studies to assess optimal hematocrit and blood pressure management during CPB, collectively these and other studies are consistent with other evidence to suggest concern over tolerance of extreme CPB anemia, and less concern over hypotension in the setting of preserved CPB flow.

With regard to anemia tolerance during CPB, numerous retrospective studies in several organ systems [8, 10, 16, 20] suggest an “inflection point” with increasing kidney and other organ dysfunction when lowest hematocrit values fall below 21% to 24% [8, 16, 21-23]. Similar studies report organ failure rates (eg, dialysis, stroke, death) with inflection points for increased occurrence at higher hematocrit values (eg, 25% to 26%) [10] or hematocrit change relative to baseline (eg, more than 50% drop) [20].

Despite numerous studies designed to better define optimal clinical practice with regard to anemia tolerance, transfusion, and blood pressure management during CPB, these questions remain incompletely answered. Given that there are (almost) no randomized studies exploring this issue to guide care, the majority of evidence on which to base practice guidelines comes from consensus opinion including review of cumulated observations from retrospective studies. Notably, such assessments often involve single organ function, which also does not always accurately predict overall outcome (eg, aprotinin, rofecoxib).

With regard to tolerating hypotension during CPB, as long as flow rate approximates 2 to 2.4L · m⁻² · min⁻¹, there is little evidence to suggest the lower blood pressures (eg, 30 to 50 mm Hg mean) are less well tolerated than higher values (eg, 60 to 80 mm Hg). Nonetheless, there is some evidence of an interaction between low blood pressure during CPB and cerebral dysfunction [6, 24]. Additionally, low blood pressure during CPB that reflected poor pump flow was associated with poorer organ outcome in one study [12]. Some investigators hypothesize that post–cardiac surgery AKI is related to chronically poor oxygen availability in the renal medulla (medullary hypoxia), which may make the kidney more vulnerable to even minor insults resulting in ischemic or inflammatory injury [25]. It should be noted that the two major determinants of oxygen delivery are blood oxygen content and pump flow. There has been some work already published suggesting an association between AKI and low oxygen delivery. Presumably, poor oxygen delivery causes organ dysoxia, leading to tissue acidosis and increased production of carbon dioxide, and ultimately increasing the risk of AKI [26].

In summary, despite using a significantly larger sample of similar cardiac surgery procedures, and exploring for associations in several different ways we could not reproduce the findings of Haase and colleagues [13]: that cardiac surgery–related AKI risk is increased with the co-occurrence of anemia and hypotension during CPB relative to anemia alone. Although our study is retrospective, these data are consistent with other studies that associate CPB anemia, but not hypotension, with increased AKI risk. Ultimately, prospective randomized studies will be needed to determine optimal hematocrit and blood pressure management during CPB.

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References
In this article, Sickeler and colleagues [1] were unable to confirm any association of cardiac operation–related acute kidney injury (AKI) risk with the co-occurrence of hypotension and anemia during cardiopulmonary bypass (CPB) relative to anemia alone. Their findings contrasted with a previous analysis by Haase and colleagues [2], who concluded that anemia might participate in renal injury during CPB and that its effect may be stronger when associated with hypotension. The readers of these conflicting observational analyses are left with the dilemma of how to guide their practice if they are to focus on one or two factors. A way to address the dilemma would be to consider a multifactorial strategy to decrease the incidence of AKI related to cardiac operations.

In the setting of the maladaptive systemic inflammatory response to CPB, adequate oxygen delivery to the renal medulla is key to decreasing the occurrence of AKI related to cardiac operations [3]. Inasmuch as AKI related to a cardiac procedure may be a marker affecting long-term survival [4], it may serve our patients well to use AKI related to cardiac operations as a guide to how well we are preparing patients for cardiac procedures and managing them intraoperatively.

Millions of years of evolution have provided us with the useful inflammatory response that, in the setting of CPB and allogeneic blood products, is maladaptive and harmful. Individual susceptibility to this exuberant level of systemic inflammation is driven by genetic polymorphism, occurring in a fraction of a percent of the genome that determines how we are different from one another. Coupling that susceptibility with poor oxygen delivery to the renal medulla drives the potential for AKI related to cardiac operations. As mentioned in the study by Sickeler and colleagues, renal blood flows initially to the renal cortex, wherein lie the glomeruli, leaving arterial blood less saturated with oxygen upon arrival at the renal medulla, where the renal tubules reside. AKI related to cardiac operations has an impact on short-term and long-term morbidity and mortality and may be a signal for injuries to other systems. There are opportunities to address anemia as well as other variables in the intraoperative phase of cardiac surgical procedures. For example, satisfying the equation for oxygen delivery to the kidneys has been shown to make a difference in the rate of AKI related to cardiac operations [3]. Inasmuch as the formula for oxygen delivery is as follows: $\text{DO}_2 = \text{pump flow} \times (\text{Hb} \times 1.36 \times \text{O}_2 \text{ sat} + 0.003 \times \text{pO}_2)$, four

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INVITED COMMENTARY

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