Nadir Hematocrit on Bypass and Rates of Acute Kidney Injury: Does Sex Matter?

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Background. **Reports have associated nadir hematocrit (Hct) on cardiopulmonary bypass with the occurrence of renal dysfunction. Recent literature has suggested that women, although more often exposed to lower nadir Hct, have a lower risk of postoperative renal dysfunction. We assessed whether this relationship held across a large multicenter registry.**

Methods. **We undertook a prospective, observational study of 15,221 nondialysis-dependent patients (10,376 male, 68.2%; 4,845 female, 31.8%) undergoing cardiac surgery between 2010 and 2014 across 26 institutions in Michigan. We calculated crude and adjusted OR between nadir Hct during cardiopulmonary bypass and stage 2 or 3 acute kidney injury (AKI), and tested the interaction of sex and nadir Hct. The predicted probability of AKI was plotted separately for men and women.**

Results. **Nadir Hct less than 21% occurred among 16.6% of patients, although less commonly among men (9.5%) than women (31.9%; $p < 0.001$). Acute kidney injury occurred among 2.7% of patients, with small absolute differences between men and women (2.6% versus 3.0%, $p = 0.20$). There was a significant interaction between sex and nadir Hct ($p = 0.009$). The effect of nadir Hct on AKI was stronger among male patients (adjusted odds ratio per 1 unit decrease in nadir Hct 1.10, 95% confidence interval: 1.05 to 1.13) than female patients (adjusted odds ratio 1.01, 95% CI: 0.96, 1.06).**

Conclusions. **Lower nadir Hct was associated with an increased risk of AKI, and the effect appears to be stronger among men than women. Understanding of the mechanism underlying this association remains uncertain, although these results suggest the need to limit exposure to lower nadir Hct, especially for male patients.**

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Acute kidney injury (AKI) occurs commonly among patients undergoing coronary artery bypass graft surgery, significantly elevating a patient's risk of morbidity and mortality, and adding nearly $20,000 of index admission expenditures per case [1–3]. Given that no proven therapies exist to improve outcomes among patients with established AKI, there is a need to identify opportunities for preventing AKI in this setting.

With some exceptions, much of the literature surrounding AKI secondary to cardiac surgery has focused on identifying preoperative risk factors for AKI. Although important for risk stratification of patients for preoperative decision making, these data have limited utility unless coupled with strategies for preventing renal injury during the surgical procedure itself. Over the last decade, investigators have studied the impact of anemia during cardiopulmonary bypass (CPB) on risk of AKI [4, 5]. Given the lower average baseline red blood cell (RBC) mass of female patients, they are exposed to lower absolute nadir hematocrit (Hct) levels secondary to hemodilution [6]. Despite this increased exposure to anemia, a recent single-center study reported equivalent AKI rates among female patients [5].

We sought to identify whether the relationship between anemia during CPB and AKI is mediated by sex. To accomplish this, we undertook a multicenter observational study of nondialysis-dependent patients undergoing cardiac surgery across 26 hospitals in Michigan.

Patients and Methods

This study was approved by the Institutional Review Board of the University of Michigan Health System (IRB

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Abbreviations and Acronyms

AKI	=	acute kidney injury
CI	=	confidence interval
CPB	=	cardiopulmonary bypass
Hct	=	hematocrit
MSTCVS-QC	=	Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative
OR	=	odds ratio
PERForm	=	Perfusion Measures and Outcomes
RAP	=	retrograde autologous priming
RBC	=	red blood cell

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Patient Population

The Perfusion Measures and Outcomes (PERForm) registry is organizationally structured within the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative (MSTCVS-QC). At the time of this publication, 27 of 33 hospitals participating in the MSTCVS-QC contributed data to the PERForm registry, with an additional eight centers located outside of Michigan [7, 8]. The MSTCVS-QC began in 2001 as a cardiac surgeon-led quality collaborative embedded in the MSTCVS, and in 2005, it became partially funded by the Blue Cross/Blue Shield of Michigan insurance company. The collaborative meets quarterly to review various processes and outcomes, and to facilitate and evaluate quality improvement studies.

All programs in the MSTCVS-QC utilize The Society of Thoracic Surgeons data collection forms and submit data on a quarterly basis to both the Society database and the MSTCVS-QC data warehouse. The PERForm registry contains information related to the care and conduct of cardiovascular perfusion practices. (A list of fields and definitions may be found at http://www.mstcvsqualitycollaborative.org/perform-registry.) Each surgical record is merged with a record from the PERForm registry [9]. Participating sites are routinely audited for data validity and accuracy as part of the MSTCVS-QC audit system.

We included patients who underwent cardiac surgery at any of the 26 medical centers participating in the PERForm registry between 2010 and 2014. We excluded patients presenting with dialysis preoperatively, and patients undergoing cardiac transplantation, patients undergoing cardiopulmonary bypass with circulatory arrest, and patients having a procedure involving a ventricular assist device.

Measures

The primary outcome for this analysis was stage 2 or 3 AKI, using the Acute Kidney Injury Network creatinine criteria (defined as a twofold or greater increase in serum creatinine from baseline, creatinine rise to 4.0 mg/dL or more with an acute increase of more than 0.5 mg/dL, or acute dialysis requirement) [10]. We additionally report crude rates of transfusions, inhospital operative mortality, reoperation for bleeding, prolonged ventilation time longer than 24 hours, adverse coagulation event, total intensive care unit stay longer than 24 hours, postoperative length of stay, and 30-day readmission.

Statistical Analyses

Standard statistical tests were used, including χ^2 tests for categoric data and two-sided Wilcoxon rank-sum tests for nonnormally distributed continuous variables. Trends in patient characteristics, processes of care, and clinical outcomes were tested using nonparametric tests of trend.

We calculated crude and adjusted (age, diabetes mellitus, creatinine, vascular disease, acuity, body surface area, congestive heart failure, preoperative albumin, procedure, cross clamp duration, cardiopulmonary bypass duration, volume of acute normovolemic hemodilution, net prime volume indexed to body surface area, lowest core temperature during bypass, and RBC transfusion) odds ratio (OR) between nadir Hct during cardiopulmonary bypass and AKI, and tested the interaction of sex and nadir Hct. Generalized linear mixed effect models with a logit link were used for the adjusted analyses, where centers were included as a random effect and patient characteristics as well as surgery year were modeled as fixed effects. The effect of nadir Hct on AKI is reported as the OR per 1 unit decrease in nadir Hct. The predicted probability of AKI fixing the adjusted covariates at the average, along with 95% confidence intervals, was plotted separately for men and women.

To further explore whether intraoperative RBC transfusion moderated the relationship between nadir Hct and AKI for male and female patients, separate analyses were carried out for patients with and patients without intraoperative RBC transfusion using generalized linear mixed effect models, as described above. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). The tests were considered significant at p less than 0.05.

Results

During the study period, 17,292 patients underwent cardiac surgery within the participating centers. After excluding patients undergoing circulatory arrest (n = 847), cardiac transplantation (n = 88), use of a ventricular assist device (n = 383), and patients with missing data regarding Hct during CPB or occurrence of AKI (n = 434), as well as those presenting preoperatively with dialysis (n = 319), the final cohort consisted of 15,221 patients (10,376 male, 4,845 female).

Preoperative patient characteristics are listed in Table 1. There were a significantly higher number of women in the greater than 70 years age bracket. Female patients also tended to have a lower body surface area compared with their male counterparts. Preoperative rates of diabetes mellitus, vascular disease, and hypertension were similar between male and female patients, whereas there was a significantly higher rate of chronic