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Hemodynamic Determinants of Cardiac Surgery-Associated Acute Kidney Injury

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OBJECTIVES: Examine the: 1) relative role of hemodynamic determinants of acute kidney injury (AKI) obtained in the immediate postcardiac surgery setting compared with established risk factors, 2) their predictive value, and 3) extent mediation via central venous pressure (CVP) and mean arterial pressure (MAP).

DESIGN: Retrospective observational study. The main outcome of the study was moderate to severe AKI, per kidney disease: improving global outcomes, within 14 days of surgery.

SETTING: U.S. academic medical center.

PATIENTS: Adult patients undergoing cardiac surgery between January 2000 and December 2019 ($n = 40,426$) in a single U.S.-based medical center. Pulmonary artery catheter measurements were performed at a median of 102 minutes (11, 132) following cardiopulmonary bypass discontinuation.

INTERVENTIONS: None.

MEASUREMENTS AND RESULTS: The median age of the cohort was 67 years (58, 75), and 33% were female; 70% had chronic hypertension, 29% had congestive heart failure, and 3% had chronic kidney disease. In a multivariable model, which included comorbidities and traditional intraoperative risk factors, CVP ($p < 0.0001$), heart rate ($p < 0.0001$), cardiac index ($p < 0.0001$), and MAP ($p < 0.0001$), were strong predictors of AKI, and superseded factors such as surgery type and cardiopulmonary bypass duration. The cardiac index had a significant interaction with heart rate ($p = 0.026$); a faster heart rate had a differentiating effect on the relationship of cardiac index with AKI, where a higher heart rate heightened the risk of AKI primarily in patients with low cardiac output. There was also significant interaction observed between CVP and MAP ($p = 0.009$); where the combination of elevated CVP and low MAP had a synergistic effect on AKI incidence.

CONCLUSIONS: Hemodynamic factors measured within a few hours of surgery showed a strong association with AKI. Furthermore, determinants of kidney perfusion, namely CVP and arterial pressure are interdependent; as are constituents of stroke volume, that is, cardiac output and heart rate.

KEYWORDS: acute kidney injury; cardiac index; cardiac surgery; central venous pressure; heart rate; mean arterial pressure

Acute kidney injury (AKI) is a common complication after cardiac surgery and is associated with short- and long-term morbidity and mortality (1–3). To date, there are no primary or secondary curative interventions for cardiac surgery-associated AKI (CS-AKI); preventive and supportive strategies remain the mainstay of care. The Society of Thoracic Surgeons guidelines only include two class 1 recommendations regarding CS-AKI which address intraoperative oxygen delivery and temperature management strategies during surgery.

Recent efforts have focused on the identification of high-risk patients in the immediate postoperative period and the implementation of goal-targeted

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KEY POINTS

Question: Which hemodynamic parameters measured immediately postcardiac surgery are associated with acute kidney injury (AKI)?

Findings: Cardiac index, central venous pressure (CVP), heart rate, and mean arterial pressure measured in 40,426 patients postcardiac surgery were strongly associated with AKI, after accounting for baseline comorbidities and intraoperative risk factors. Furthermore, determinants of kidney perfusion, namely CVP and arterial pressure are interdependent; as are determinants of stroke volume, that is, cardiac output and heart rate.

Meaning: The current findings may guide future prospective studies that explore hemodynamic targets that optimize renal and other end-organ perfusion in postcardiac surgery patients.

interventions such as the kidney disease improving global outcomes (KDIGO) care bundle (4–6). The bundle includes mostly passive measures such as close monitoring of kidney function and avoidance of nephrotoxic stressors but also recommends hemodynamic optimization (7). In a systematic review of noncardiac surgery patients, the use of different hemodynamic optimization methods targeted to increase global blood flow reduced rates of AKI (8). However, specific hemodynamic targets in cardiac surgery patients at high risk for CS-AKI have not been systematically evaluated.

The current study sought to examine the: 1) the relative role of hemodynamic determinants of AKI obtained in the immediate postcardiac surgery setting compared with preexisting clinical and intraoperative risk factors, 2) their added predictive value to an externally validated model, and 3) the extent of hemodynamic effects mediated via central venous pressure (CVP) and mean arterial pressure (MAP).

MATERIALS AND METHODS

The study was approved by the institutional review (IRB) of Cleveland Clinic (IRB number 10-739, "ARF postopen heart surgery," with active status till August 29, 2023), and the requirement for informed consent was exempted due to its minimal risk nature. All procedures in the current study were conducted in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975. Adult patients undergoing cardiovascular surgery between the years 2000 and 2019 were included in the current retrospective analysis. Surgical data were obtained from the Anesthesiology Institute Patient Registry and were supplemented with laboratory data retrieved from electronic medical records. Patient comorbidities and procedures were characterized using the *International Classification of Diseases*, Ninth and Tenth Revisions (ICD-9 and ICD-10).

All adults (≥ 18 yr) who underwent coronary artery bypass graft, valve, or aorta surgery were included from a single U.S.-based medical center. Valve surgery included aortic, mitral, pulmonary, and tricuspid valve surgery. Aorta surgery included root, ascending, and thoracoabdominal surgery. Patients with end-stage kidney failure required preoperative dialysis within 6 months before or on the day of surgery or had preoperative serum creatinine values of 4 mg/dL or greater were excluded (**Fig. 1**).

The outcome measure was defined using a modified KDIGO creatinine-based definition for AKI diagnosis, using the most recent serum creatinine before surgery for baseline. Moderate to severe AKI (stage 2 or worse per KDIGO classification) within 2 weeks of surgery was the primary endpoint for the study (or earlier in the case of discharge). Patient follow-up concluded at the end of January 2020.

All hemodynamic measurements were performed via pulmonary artery catheter following surgical closure and arrival to the ICU. Cardiac output was determined by calculation using the Fick method by sampling mixed central venous blood gas from the pulmonary artery. The systemic blood pressures were measured via an arterial catheter. Pulmonary artery occlusion pressure was not included due to the high rate of missing values.

Analysis of hemodynamic parameters was evaluated in the context of preoperative clinical and intraoperative risk factors associated with AKI. Clinical factors included diabetes mellitus, heart failure, hypertension, kidney disease, lung disease, and left ventricular ejection fraction less than or equal to 45%; intraoperative factors included type of surgery, intraoperative-packed RBC transfusion, cardiopulmonary bypass duration, and vasopressor use.

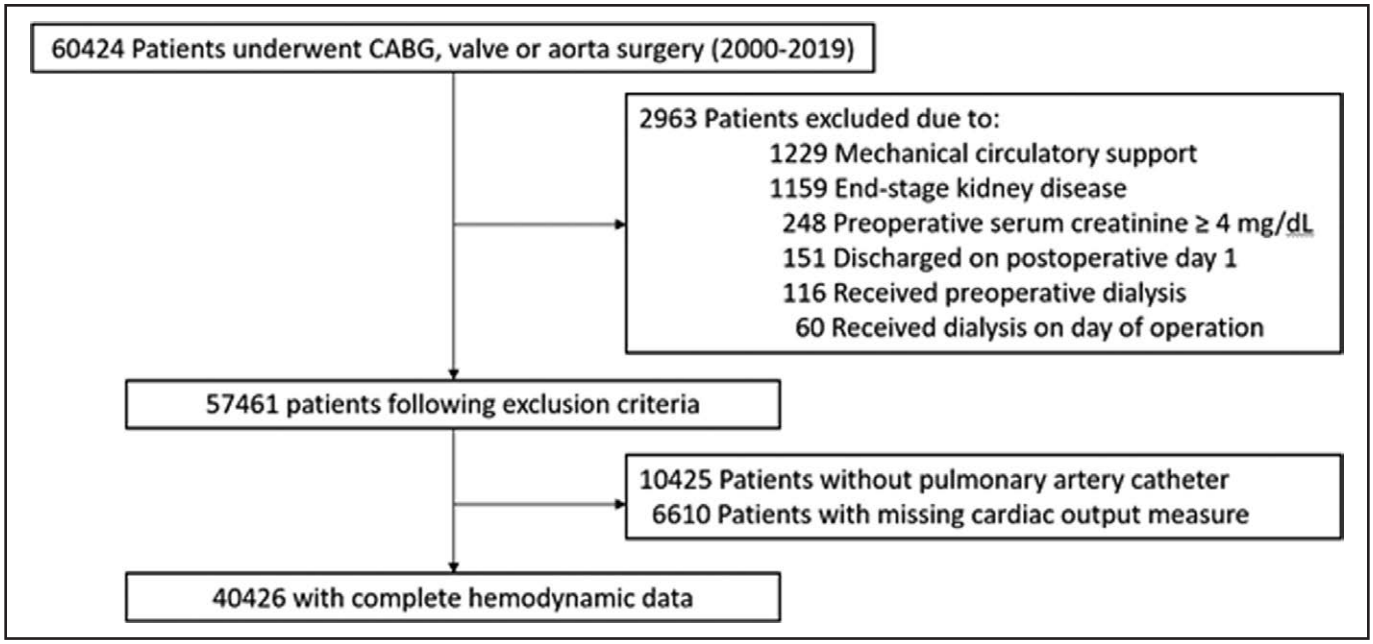

Figure 1. Cohort selection flowchart. Mechanical circulatory support includes intra-arterial balloon pump and percutaneous and extracorporeal assist devices. CABG = coronary artery bypass graft surgery.

Mediation analysis was performed to provide a statistical framework to test the role of CVP and MAP as mediators of more distal hemodynamic parameters involved in kidney perfusion. Mediation can show if an association is completely or partially mediated by one or multiple mediators. It can also give an estimate of the association of the effect with the endpoint explained through the mediator(s), and that of the direct effect on the outcome if there is one.

Sensitivity analysis was performed to assess the impact of operation date (2000–2009 vs. 2010–2019) on right heart catheter use, its association with moderate to severe AKI, and its effect on hemodynamic parameters in a multivariable model.

Statistical Analysis

Continuous variables were summarized as median (25th, 75th percentiles), or as mean (SD), and categorical variables as frequency (percentile). Univariate comparisons between groups were made using the Kruskal-Wallis test, standardized mean difference, and the chi-square test. The association between moderate to severe AKI, hemodynamic indices, clinical risk factors, and their interactions were evaluated via multivariable logistic regression analysis. Continuous covariates were fitted in restricted cubic splines with three knots (at 10, 50, and 90 percentiles) to account for a nonlinear relationship with the outcome. Covariate significance was measured by computing the partial chi-square statistic, adjusted for degrees of freedom, which tests the strength of association of each predictor with the outcome within the full model. Mediation analyses were performed by the product method for direct and mediated effects. Each hemodynamic parameter was examined for mediation via CVP and MAP where both outcome and mediator models were adjusted for the remainder of hemodynamic indices. Bootstrap resampling was used to obtain standard errors and 95% CIs for the effects (9, 10).

A previously published perioperative metabolic panel-derived prediction algorithm was used as our base model to examine the added predictive value of postoperative hemodynamic indices to predict CS-AKI (6). Briefly, the metabolic model uses perioperative change in serum creatinine, and postoperative blood urea nitrogen, serum sodium, potassium, bicarbonate, and albumin from the first metabolic panel after cardiac surgery in multivariable logistic model to predict moderate to severe AKI (6). The likelihood ratio test was used to assess if hemodynamic indices add new information to the base metabolic model individually and collectively regarding the risk for moderate to severe AKI in a logistic regression analysis. The fraction of the new diagnostic information that is due to hemodynamic indices was estimated by one minus the ratio

of the variance of the base model to the variance of the combined model.

The distribution of CVP with varying risks for AKI based on the metabolic predictive model was depicted in a scatter plot, where observed AKI risk was color-coded based on the event rate estimated by each subject's 250 nearest neighbors per Mahalanobis Distance (**Supplemental Fig. 1**, http://links.lww.com/CCX/B321).

Patients with right heart catheter measurements were included in the multivariable analysis. Those with missing cardiac output measurements were excluded. Imputation of other missing hemodynamic data was performed using multiple imputation methods based on bootstrapping and predictive mean matching, where a flexible additive model is used to predict missing values (11). We performed all statistical analyses and plotted graphs using the SAS Enterprise Guide (SAS, version 8.2, Cary, NC), and the R statistical package (version 4.1.1; www.r-project.org).

RESULTS

The study consisted of 60,424 adult patients who underwent cardiac surgery. Sixty-seven percent (40,426) had indwelling pulmonary artery catheters, and nonmissing cardiac output measurement (Fig. 1). MAP, pulmonary artery systolic, and diastolic pressures were available in greater than 99% of patients; CVP and temperature were available in 92% of patients. Preoperative creatinine was available in more than 99% of patients. The median time from discontinuation of cardiopulmonary bypass to pulmonary artery catheter obtained hemodynamic data was 102 minutes (77, 132). Catheter use was more common in surgeries performed from 2000 to 2009 compared with 2010 to 2019 (85% vs. 50%, $p < 0.001$), and was associated with a higher incidence of hypertension (72% vs. 55%, $p < 0.001$), diabetes (27% vs. 15%, $p < 0.001$), congestive heart failure (29% vs. 11%, $p < 0.001$), pulmonary disease (14% vs. 11%, $p < 0.001$), and longer cardiopulmonary bypass time (77 vs. 69 min, $p < 0.001$). The median age of the cohort was 67 years (58, 75), and 33% were female; 70% had chronic hypertension, 29% had congestive heart failure, and 3% had chronic kidney disease. **Table 1** displays clinical, surgical, and hemodynamic data of patients with and without AKI.

Multivariable Analysis

Figure 2 displays the relative importance of hemodynamic parameters for AKI in the fully adjusted multivariable model, which includes established clinical and intraoperative risk factors (12, 13). Intraoperative blood transfusions were the strongest predictor of AKI in the full model. Patients who required up to two packed cell transfusions had double the risk for reoperation within 72 hours of surgery (1.3% vs. 2.4%, $p < 0.001$), and those who required more than two transfusions were at seven-fold increased risk for reoperation (1.3% vs. 9.3, $p < 0.001$) compared with those who did not receive any transfusion. As shown in **Supplemental Table 1** (http://links.lww.com/CCX/B321) number of transfusions received during surgery was associated with worse hemodynamics. Several of the hemodynamic factors, specifically CVP, heart rate, cardiac index, and MAP were strong predictors and superseded factors such as surgery type and cardiopulmonary bypass duration. Comorbidities associated with AKI included hypertension, diabetes, heart failure, obstructive lung disease, and chronic kidney disease.

Cardiac index, MAP, and pulmonary artery pulse pressure had a significant nonlinear relationship with AKI, whereas CVP, heart rate, and temperature had a significant linear association (**Fig. 3**). Cardiac index had a significant interaction with heart rate ($p = 0.026$); faster heart rate had a differentiating effect on the relationship of cardiac index with AKI, where a higher heart rate heightened risk of AKI primarily in patients with low cardiac output (**Fig. 4*A***; and **Supplemental Fig. 2*A***, http://links.lww.com/CCX/B321). There was also significant interaction observed between CVP and MAP ($p = 0.009$). The combination of elevated CVP and low MAP had a synergistic effect on AKI incidence. Patients with low CVP did not have a higher risk for AKI even with MAP in the lower range; however, those with elevated CVPs were at higher risk for AKI than baseline regardless of MAP (**Fig. 4*B***; and **Supplemental Fig. 2*B***, http://links.lww.com/CCX/B321).

In the sensitivity analysis which included year of surgery in a multivariable model of hemodynamic parameters and AKI endpoint, the use of a right heart catheter was associated with lower odds for AKI in 2010–2019 surgery years compared with 2000–2009,

TABLE 1.
Baseline Clinical Characteristics, Operative Information, and Postoperative Hemodynamic Data

Variables	No AKI (*n* = 37,840)	AKI (*n* = 2,586)	Standardized Mean Difference
Age, median (IQR), yr	67 (58, 75)	70 (61, 77)	0.17
Female, *n* (%)	12,263 (32)	1,076 (42)	0.19
Male, *n* (%)	25,577 (68)	1,510 (58)	
White[a], *n* (%)	32,909 (87)	2,040 (79)	0.30
Body mass index (IQR), kg/m^2	28 (25, 32)	29 (25, 34)	0.20
Comorbid disease, *n* (%)[b]			
Hypertension	26,109 (69)	1,989 (77)	0.21
Diabetes mellitus	9,834 (26)	993 (38)	0.24
Congestive heart failure	10,553 (28)	1,167 (45)	0.36
Left ventricular ejection fraction ≤ 45	9,685 (26)	883 (35)	0.19
Coronary artery disease	7,709 (20)	615 (24)	0.08
Pulmonary disease	5,011 (13)	563 (22)	0.23
Preoperative estimated glomerular filtration rate[c] < 60 mL/min/1.73 m^2	8,760 (23)	1,173 (44)	0.43
Operative procedure[d]			0.20
Valve surgery alone, *n* (%)	11,510 (30)	746 (29)	
CABG alone, *n* (%)	10,904 (29)	552 (21)	
Aorta surgery, *n* (%)	7,652 (20)	633 (24)	
CABG and valve surgery, *n* (%)	7,774 (21)	655 (25)	
Cardiopulmonary bypass time, min	99 (73, 129)	125 (91, 169)	0.47
Packed RBC transfusions, *n* (%)			0.70
None	25,480 (67)	978 (38)	
1 or 2	7,510 (20)	590 (23)	
> 2	4,850 (13)	1,018 (39)	
Urine output	858 (600, 1,200)	735 (450, 1,100)	0.21
Hemodynamic data			
Duration from bypass end to hemodynamic data, min	101 (76, 130)	123 (91, 166)	0.46
Cardiac index, L/min/m^2	2.6 (2.2, 3.1)	2.4 (2.1, 2.9)	0.13
Central venous pressure, mm Hg	10 (7, 13)	11 (8, 15)	0.35
Heart rate, beats/min	81 (75, 90)	83 (78, 93)	0.22
Mean arterial pressure, mm Hg	79 (71, 87)	77 (69, 86)	0.10
Pulmonary artery pulse pressure, mm Hg	16 (12, 21)	18 (13, 24)	0.23

AKI = acute kidney injury, CABG = coronary artery bypass graft surgery, IQR = interquartile range (25th, 75th).

[a]Race information was obtained based on self-identification using fixed categories, retrieved from medical records.

[b]Comorbid disease was assessed using the *International Classification of Diseases*, Ninth and Tenth Revisions codes.

[c]Estimated glomerular filtration rate was calculated by creatinine-based chronic kidney disease epidemiology collaboration formula without race.

[d]Aorta surgery included root, ascending, and thoracoabdominal aortic surgery. Valve surgery included aortic, mitral, pulmonary, and tricuspid valve surgery.

Standardized mean difference (values > 0.1 are considered significant).

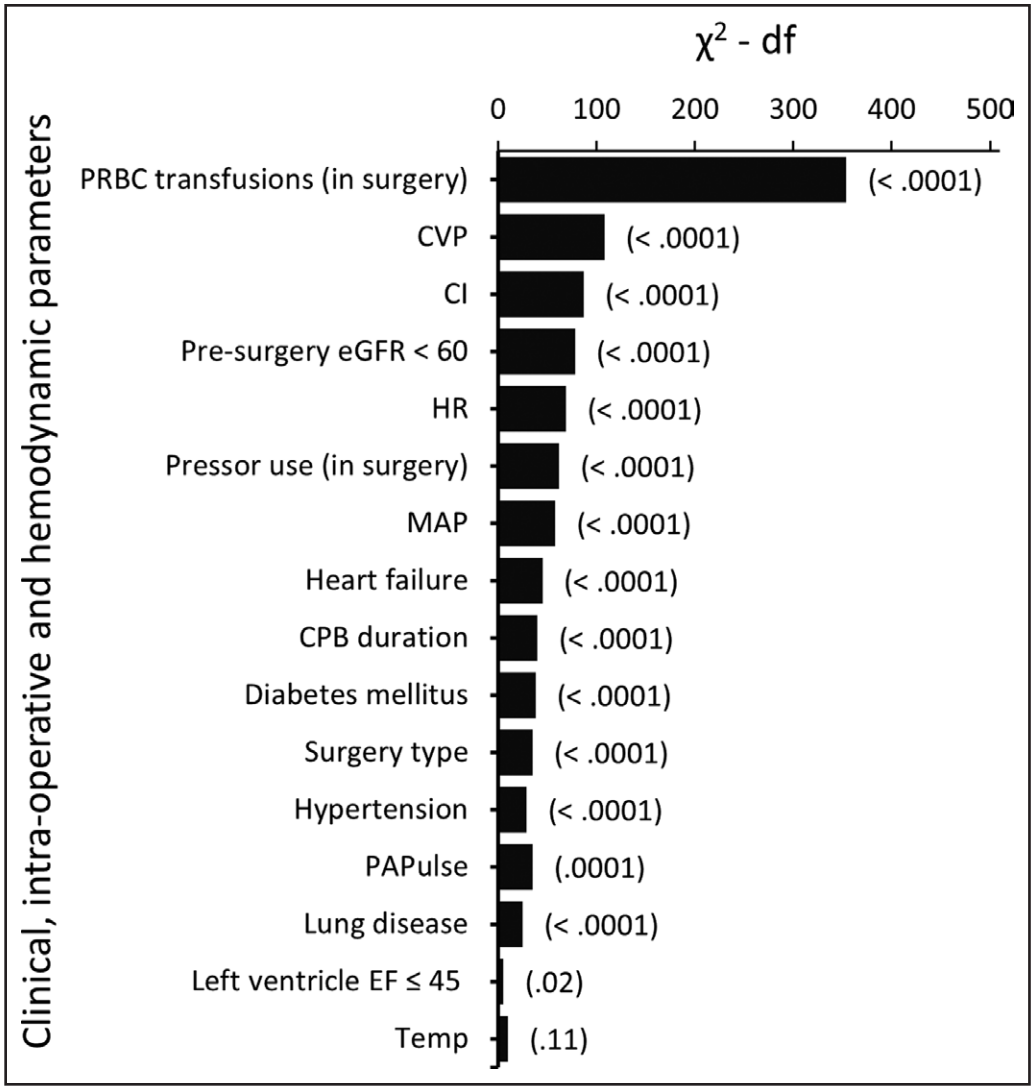

Figure 2. Performance of hemodynamic indices within the fully adjusted model. Surgery type denotes operative procedure. A higher Chi-square score minus degrees of freedom (*df*) of an individual covariate denotes its relative importance in the model. CI = cardiac index, CPB = cardiopulmonary bypass, CVP = central venous pressure, EF = ejection fraction, eGFR = estimated glomerular filtration rate (calculated per serum creatinine-based chronic kidney disease epidemiology collaboration equation without race), HR = heart rate, MAP = mean arterial pressure, PAPP = pulmonary artery pulse pressure, PRBC = packed red blood cells, Temp = temperature.

odds ratio 0.88 (95% CI, 0.81–0.95). Furthermore, the inclusion of year of surgery in the multivariable model did not change the magnitude or the direction of the association of individual hemodynamic parameters with AKI.

Mediation Analysis

Mediation analysis results are summarized in **Table 2**. Twenty-one percent of pulmonary artery pulse pressure, 10% of temperature, 6% of heart rate, and 3% of cardiac index indirect effects were transmitted via CVP on AKI, whereas only 4% of heart rate's indirect effect on AKI was mediated via MAP.

Added Value Analysis

The likelihood ratio test for added value comparing the log-likelihood of the base metabolic model to the combination of metabolic and hemodynamic model was significant for all hemodynamic indices (**Supplemental Table 2**, http://links.lww.com/CCX/B321). This presents strong evidence that the hemodynamic data adds significant diagnostic value to the metabolic predictive model. The relative explained variation of the multivariate hemodynamic model was 10% compared with the base model alone (Supplemental Table 2, http://links.lww.com/CCX/B321). The area under the curve of the base metabolic model was 0.855 (95% CI, 0.848–0.862), and 0.862 (95% CI, 0.855–0.869) of the combined hemodynamic and metabolic model with a significant difference of 0.007 (95% CI, 0.0046–0.0084).

DISCUSSION

Hemodynamic indices measured in the immediate postcardiac surgery setting were independently associated with AKI. Elevated CVP showed a strong association with AKI, and had a significant interaction with MAP. Similarly, cardiac index had a strong association

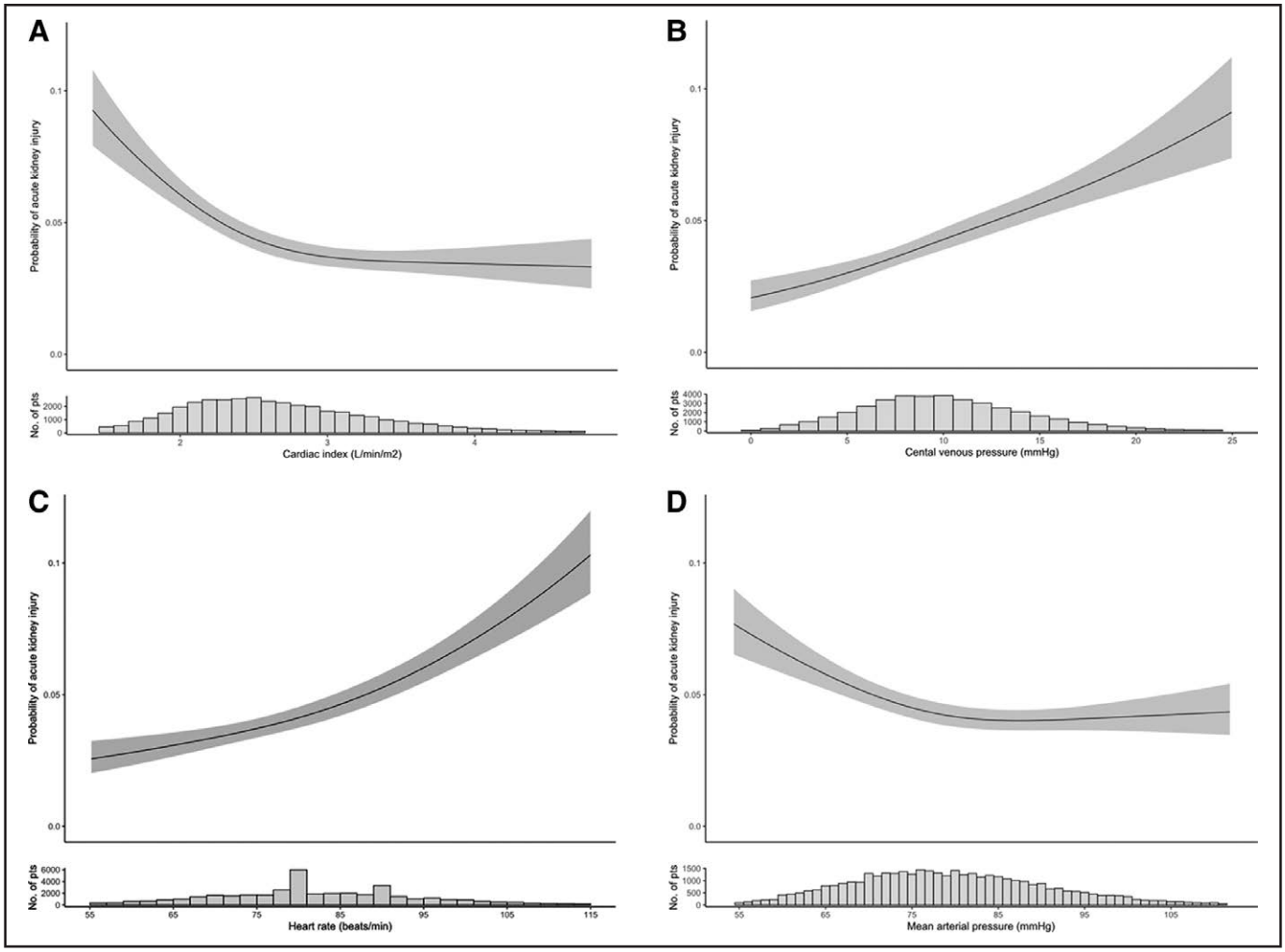

Figure 3. Adjusted probability for moderate to severe acute kidney injury within 2 weeks of cardiac surgery according to: cardiac index (**A**), central venous pressure (**B**), heart rate (**C**), and mean arterial pressure (**D**). The *shaded areas* represent 95% CI, based on the multivariable logistic regression model. The probability of the outcome for each variable was adjusted for the median values of other variables in the model: cardiac index of 2.6 L/min/m^2, central venous pressure of 10 mm Hg, heart rate of 80 beats/min, mean arterial pressure of 79 mm Hg and pulmonary artery pulse pressure of 16 mm Hg. Histograms demonstrate covariate distribution along the shared *x*-axis.

with AKI, and its effect was modified by heart rate. Hemodynamic data had a statistically significant but modest contribution in predicting AKI when added to a predictive model based on metabolic parameters.

With the exception of intraoperative blood product transfusions, hemodynamic indices had a stronger association with AKI compared with traditional preexisting and intraoperative risk factors such as chronic kidney disease and duration of cardiopulmonary bypass. Elevated CVP and low cardiac index had the strongest association with AKI, followed by hypotension and tachycardia. An increase in CVP had a linear relationship with AKI across the range examined, and its effect was further amplified if coupled with hypotension. The combination of low cardiac output and tachycardia was also associated with a heightened effect on AKI risk, likely due to a compromise in stroke volume. Mediation analysis showed that only one-tenth of heart rate, and less than 5% of cardiac output effects were transmitted via ventral venous or MAP, whereas a significant amount of pulmonary artery pulse pressure and temperature effect on AKI were mediated via CVP. These findings underscore the interplay of several hemodynamic factors as patients come off cardiopulmonary bypass, and how a variety of hemodynamic combinations may lead to AKI (14). However, regardless of the underlying driving forces, the pressure gradient

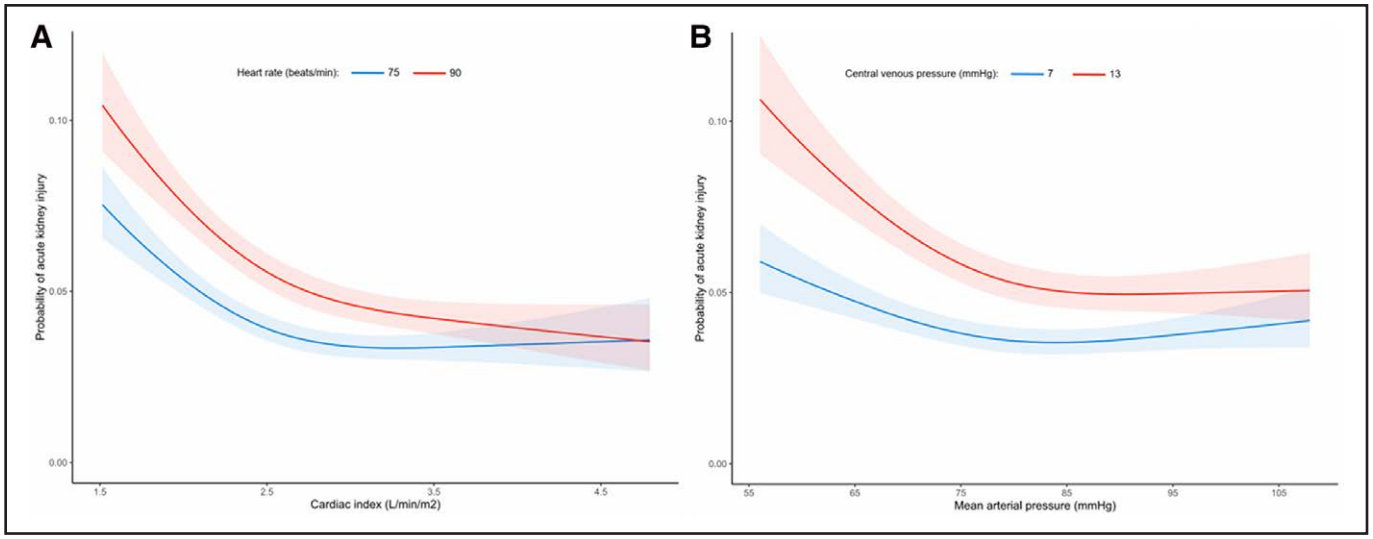

Figure 4. Adjusted probability for moderate to severe acute kidney injury within 2 weeks of cardiac surgery depicting the interaction of cardiac index and heart rate (**A**), and mean arterial pressure and central venous pressure (**B**). The *shaded areas* represent 95% CI, based on the multivariable logistic regression model. The probability of the outcome for each variable was adjusted for the median values of other variables in the model: cardiac index of 2.6 L/min/m^2, central venous pressure of 10 mm Hg, heart rate of 80 beats/min, mean arterial pressure of 79 mm Hg and pulmonary artery pulse pressure of 16 mm Hg.

TABLE 2.
Mediation Analyses of Adjusted Hemodynamic Risk Factors for Acute Kidney Injury Mediated via Central Venous Pressure, and Mean Arterial Pressure

Risk Factor	Direct Effect	Mediator	Mediated Effects	% Mediated
Cardiac index	−0.3674 (−0.4297, −0.3052)	CVP	0.0098 (0.0045, 0.0163)	3
		MAP	0.0007 (−0.0014, 0.0029)	0.2
Heart rate	0.0235 (0.0205, 0.0265)	CVP	−0.0013 (−0.0016, −0.0010)	6
		MAP	−0.0008 (−0.0011, −0.0006)	4
Pulmonary artery pulse pressure	0.0302 (0.0253, 0.0351)	CVP	0.0078 (0.0067, 0.0089)	21
		MAP	−0.0004 (−0.0007, −0.0002)	1
Temp	−0.1841 (−0.2367, −0.1315)	CVP	0.0166 (0.0115, 0.0222)	10
		MAP	−0.0015 (−0.0037, 0.0006)	1

CVP = central venous pressure, MAP = mean arterial pressure.
All mediation measures (direct and mediated effects) are defined on a log odds ratio scale for a unit change in the risk factor. Risk factors and mediators were adjusted for the remainder of the hemodynamic variables. Delta method was used for the mediation analysis, and the bootstrap method was used with 10,000 replications for the calculation of 95% CI of direct and indirect effects; the effect is not significant if the 95% CI includes zero.

across the kidney plays an important role in triggering compensatory mechanisms and determining forward flow (15–17). Particularly when we consider that like the brain kidneys are encapsulated organs with a steep pressure–volume relationship that compromises organ blood flow (18).

Elevated CVP has been shown to play a central role in the management of heart-kidney dysregulation in patients with decompensated heart failure (15, 19–21). Others have shown that elevated CVP was also associated with the risk of developing new or persistent AKI in critically ill septic patients, and called to question the practice of targeting high CVP goals for volume resuscitation (22, 23). Decongestion at the expense of lower systemic arterial pressures however can lead to adverse kidney outcomes (24). In patients

undergoing noncardiac surgery at Cleveland Clinic, even a short duration of intraoperative MAP less than 55 mm Hg was associated with AKI and myocardial infarction (25). Similarly, therapeutic agents studied in cardiac surgery such as fenoldopam, a dopamine 1 receptor agonist, did not reduce the need for AKI requiring dialysis likely due to the increased rate of hypotension in the intervention group (26). Furthermore, targeting higher MAP has improved kidney outcomes in septic patients with cardiovascular disease, and in hepatorenal syndrome (27, 28). In cardiac surgery patients with postoperative vasoplegia, vasopressin compared with norepinephrine use achieved higher MAPs and demonstrated a significantly better primary composite outcome; an effect is primarily driven by lower incidence of AKI, and dialysis requirement (29)

The pattern of the interaction observed between CVP and MAP in the current study may explain why some studies investigating congestive kidney impairment failed to show the role of arterial pressure; where the ideal goal arterial pressure for an individual patient is not static but dependent on the patient's venous pressure (20, 21, 30). Other reports emphasized the importance of perfusion pressure (arterial pressure–venous pressure) on AKI incidence in the setting of heart failure and cardiac surgery (31–34). However, in the current study, patients with elevated CVP with adequate MAP remained at a lower but still increased risk for AKI compared with patients with low CVPs. Furthermore, FR Winton in an elegant series of animal experiments has shown that blood flow through the kidney is reduced more by an increase in venous pressure than by an equivalent decrease in arterial pressure (15). Therefore, a summary measure such as perfusion pressure, although it incorporates two important physiologic measures of kidney performance, undermines the importance of isolated high venous pressure, and inaccurately gives equal weight to venous and arterial pressures.

Within the hemodynamic indices, CVP had the largest added predictive value to a previously validated perioperative metabolic predictive model. However, there was only a modest gain to area under the curve when hemodynamic factors were added to the metabolic model (6). Considering that right heart catheterization is no longer routine practice in cardiac surgery settings, along with the only modest improvement in discrimination, the inclusion of hemodynamic parameters to the previously validated metabolic-based models is not warranted.

The study has limitations. The findings presented in this study are associations and do not imply causation due to the observational nature of the study. Second, the current study does not investigate the optimization of the aforementioned hemodynamic indices by interventions targeting intravascular volume, cardiac output, right ventricle compliance, intrathoracic pressure, or vascular tone. However, it makes the assertion that irrespective of the underlying cause(s), an unfavorable combination of MAP and CVP along with compromised stroke volume, is associated with heightened AKI risk. Third, the current study is limited to observations made on hemodynamic parameters measured only at a single time point postcardiac surgery, and renal blood flow was not directly measured.

In conclusion, hemodynamic factors, in particular, CVP, cardiac output, MAP, and heart rate showed a strong association with AKI. Furthermore, determinants of kidney perfusion, namely CVP and arterial pressure are interdependent; as are constituents of stroke volume, that is, cardiac output and heart rate. These observational findings may guide future prospective studies that explore hemodynamic targets that optimize renal and other end-organ perfusion.

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Drs. Demirjian and Insler were involved in the concept and design. Dr. Demirjian was involved in the drafting of the article. Drs. Gadegbeku, Gillinov, and Insler were involved in administrative, technical, or material support and supervision. All authors were involved in the acquisition, analysis, or interpretation of data, and critical revision of the article for important intellectual content. All authors read and approved the final article.

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Dr. Demirjian and Cleveland Clinic Innovations Center hold U.S. patents for predictive models for cardiac surgery-associated acute kidney injury. Dr. Demirjian reported receiving

speaker fees from Outset Medical, Baxter, BioMerieux, and Astute Medical outside the submitted work. Dr. Tang is a consultant for Sequana Medical, Cardiol Therapeutics, Genomics plc, Renovacor, Zehna Therapeutics, WhiteSwell, Boston Scientific, and Kiniksa, and has received an honorarium from Springer Nature and American Board of Internal Medicine. Dr. Gillinov is a consultant for Edwards, Medtronic, Artivion, Abbott, ClearFlow, and AtriCure companies. The remaining authors have nothing to disclose.

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REFERENCES

1. Brown JR, Baker RA, Shore-Lesserson L, et al: The Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology Clinical Practice Guidelines for the prevention of adult cardiac surgery-associated acute kidney injury. *Ann Thorac Surg* 2023; 115:34–42
2. Hobson CE, Yavas S, Segal MS, et al: Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation* 2009; 119:2444–2453
3. Lafrance JP, Miller DR: Acute kidney injury associated with increased long-term mortality. *J Am Soc Nephrol* 2010; 21:345–352
4. Meersch M, Schmidt C, Hoffmeier A, et al: Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: The PrevAKI randomized controlled trial. *Intensive Care Med* 2017; 43:1551–1561
5. Ostermann M, Lumlertgul N, Wilson FP: Predictive models for acute kidney injury following cardiac surgery: The importance of accurate and actionable prediction. *JAMA* 2022; 327:927–929
6. Demirjian S, Bashour CA, Shaw A, et al: Predictive accuracy of a perioperative laboratory test-based prediction model for moderate to severe acute kidney injury after cardiac surgery. *JAMA* 2022; 327:956–964
7. Palevsky PM, Liu KD, Brophy PD, et al: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis* 2013; 61:649–672
8. Grocott MP, Dushianthan A, Hamilton MA, et al; Optimisation Systematic Review Steering Group: Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery. *Cochrane Database Syst Rev* 2012; 11:CD004082
9. Hayes AF: *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. New York, NY, US, Guilford Press, 2013
10. Cheng C, Spiegelman D, Li F: Estimating the natural indirect effect and the mediation proportion via the product method. *BMC Med Res Methodol* 2021; 21:253
11. Van Buuren S: *Flexible Imputation of Missing Data*. Boca Raton, Fl, CRC Press, 2018
12. Thakar CV, Arrigain S, Worley S, et al: A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol* 2005; 16:162–168
13. Demirjian S, Schold JD, Navia J, et al: Predictive models for acute kidney injury following cardiac surgery. *Am J Kidney Dis* 2012; 59:382–389
14. Testani JM, Khera AV, St John Sutton MG, et al: Effect of right ventricular function and venous congestion on cardiorenal interactions during the treatment of decompensated heart failure. *Am J Cardiol* 2010; 105:511–516
15. Winton FR: The influence of venous pressure on the isolated mammalian kidney. *J Physiol* 1931; 72:49–61
16. Schweda F, Segerer F, Castrop H, et al: Blood pressure-dependent inhibition of Renin secretion requires A1 adenosine receptors. *Hypertension* 2005; 46:780–786
17. Yip KP, Balasubramanian L, Kan C, et al: Intraluminal pressure triggers myogenic response via activation of calcium spark and calcium-activated chloride channel in rat renal afferent arteriole. *Am J Physiol Renal Physiol* 2018; 315:F1592–F1600
18. Khraibi AA, Knox FG: Effect of renal decapsulation on renal interstitial hydrostatic pressure and natriuresis. *Am J Physiol* 1989; 257:R44–R48
19. Damman K, Navis G, Smilde TD, et al: Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. *Eur J Heart Fail* 2007; 9:872–878
20. Mullens W, Abrahams Z, Francis GS, et al: Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 2009; 53:589–596
21. Hanberg JS, Sury K, Wilson FP, et al: Reduced cardiac index is not the dominant driver of renal dysfunction in heart failure. *J Am Coll Cardiol* 2016; 67:2199–2208
22. Maitland K, Kiguli S, Opoka RO, et al; FEAST Trial Group: Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011; 364:2483–2495
23. Legrand M, Dupuis C, Simon C, et al: Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: A retrospective observational study. *Crit Care* 2013; 17:R278
24. Dupont M, Mullens W, Finucan M, et al: Determinants of dynamic changes in serum creatinine in acute decompensated heart failure: The importance of blood pressure reduction during treatment. *Eur J Heart Fail* 2013; 15:433–440
25. Walsh M, Devereaux PJ, Garg AX, et al: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical definition of hypotension. *Anesthesiology* 2013; 119:507–515
26. Bove T, Zangrillo A, Guarracino F, et al: Effect of fenoldopam on use of renal replacement therapy among patients with acute kidney injury after cardiac surgery: A randomized clinical trial. *JAMA* 2014; 312:2244–2253
27. Asfar P, Meziani F, Hamel JF, et al; SEPSISPAM Investigators: High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014; 370:1583–1593
28. Wong F, Pappas SC, Curry MP, et al; CONFIRM Study Investigators: Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. *N Engl J Med* 2021; 384:818–828

29. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, et al: Vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery: The VANCS randomized controlled trial. *Anesthesiology* 2017; 126:85–93
30. Guglin M, Rivero A, Matar F, et al: Renal dysfunction in heart failure is due to congestion but not low output. *Clin Cardiol* 2011; 34:113–116
31. Wehbe E, Patarroyo M, Taliercio JJ, et al: Renal failure requiring dialysis complicating slow continuous ultrafiltration in acute heart failure: Importance of systolic perfusion pressure. *J Card Fail* 2015; 21:108–115
32. Jin J, Yu J, Chang SC, et al: Postoperative diastolic perfusion pressure is associated with the development of acute kidney injury in patients after cardiac surgery: A retrospective analysis. *BMC Nephrol* 2019; 20:458
33. Hu R, Kalam Y, Broad J, et al: Decreased mean perfusion pressure as an independent predictor of acute kidney injury after cardiac surgery. *Heart Vessels* 2020; 35:1154–1163
34. Kotani Y, Yoshida T, Kumasawa J, et al: The impact of relative hypotension on acute kidney injury progression after cardiac surgery: A multicenter retrospective cohort study. *Ann Intensive Care* 2021; 11:178