ANESTHESIOLOGY

Defining an Intraoperative Hypotension Threshold in Association with *De Novo* Renal Replacement Therapy after Cardiac Surgery

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ANESTHESIOLOGY 2020; 132:1447–57

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Patients undergoing cardiac surgery with cardiopulmonary bypass are at risk for acute kidney injury requiring *de novo* renal replacement therapy
- The specific association between pre–, during, and post–cardiopulmonary bypass hypotension and *de novo* renal replacement therapy remains unclear

What This Article Tells Us That Is New

- Varying definitions of hypotension before and during cardiopulmonary bypass are not associated with renal replacement therapy
- Mean arterial pressure less than 55 or between 55 and 64 mmHg for 10 or more minutes after cardiopulmonary bypass is associated with renal replacement therapy
- The association of post–cardiopulmonary bypass hypotension with renal replacement therapy is weaker than nonmodifiable procedure and patient risk factors

ABSTRACT

Background: Acute kidney injury (AKI) is a frequent and deadly complication after cardiac surgery. In the absence of effective therapies, a focus on risk factor identification and modification has been the mainstay of management. The authors sought to determine the impact of intraoperative hypotension on *de novo* postoperative renal replacement therapy in patients undergoing cardiac surgery, hypothesizing that prolonged periods of hypotension during and after cardiopulmonary bypass (CPB) were associated with an increased risk of renal replacement therapy.

Methods: Included in this single-center retrospective cohort study were adult patients who underwent cardiac surgery requiring CPB between November 2009 and April 2015. Excluded were patients who were dialysis dependent, underwent thoracic aorta or off-pump procedures, or died before receiving renal replacement therapy. Degrees of hypotension were defined by mean arterial pressure (MAP) as less than 55, 55 to 64, and 65 to 74 mmHg before, during, and after CPB. The primary outcome was *de novo* renal replacement therapy.

Results: Of 6,523 patient records, 336 (5.2%) required new postoperative renal replacement therapy. Each 10-min epoch of MAP less than 55 mmHg post-CPB was associated with an adjusted odds ratio of 1.13 (95% CI, 1.05 to 1.23; $P = 0.002$), and each 10-min epoch of MAP between 55 and 64 mmHg post-CPB was associated with an adjusted odds ratio of 1.12 (95% CI, 1.06 to 1.18; $P = 0.0001$) for renal replacement therapy. The authors did not observe an association between hypotension before and during CPB with renal replacement therapy.

Conclusions: MAP less than 65 mmHg for 10 min or more post-CPB is associated with an increased risk of *de novo* postoperative renal replacement therapy. The association between intraoperative hypotension and AKI was weaker in comparison to factors such as renal insufficiency, heart failure, obesity, anemia, complex or emergent surgery, and new-onset postoperative atrial fibrillation. Nonetheless, post-CPB hypotension is a potentially easier modifiable risk factor that warrants further investigation.

(ANESTHESIOLOGY 2020; 132:1447–57)

Despite steady improvements in surgical, anesthetic, and perioperative care, cardiac surgery–associated acute kidney injury (AKI) remains a frequent and deadly complication, with a pooled incidence rate of 22.3%.[1] AKI after cardiac surgery is associated with both short- and long-term morbidity and mortality,[1] prolonged intensive care unit (ICU) and hospital stay, and increased healthcare costs.[1] Even small transient increases in postoperative creatinine are associated with adverse outcomes[2,3] and decreased patient survival.[4] Severe AKI requiring postoperative renal replacement therapy occurs in 1 to 6% of cardiac surgery patients,[5] and confers an eightfold increase in the odds of death.[6] In the absence of effective therapies,[7–9] a focus on

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Part of the work presented in this article has been presented at the American Heart Association Scientific Sessions in Anaheim, California, November 11 to 15, 2017. J.M.C.N. and H.J. contributed equally to this article.

Submitted for publication January 5, 2019. Accepted for publication February 14, 2020. Published online first on March 19, 2020. From the Division of Cardiac Surgery (J.M.C.N., H.J., M. Boodhwani, M.R.) and the Division of Cardiac Anesthesiology (A.M.C., M. Bourke, L.Y.S.), Cardiocore Big Data Research Unit (L.Y.S.), University of Ottawa Heart Institute, Ottawa, Canada; the School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada (L.Y.S.), and the Cardiovascular Research Program, Institute for Clinical Evaluative Sciences, Toronto, Canada (L.Y.S.).

 Anesthesiology 2020; 132:1447–57. DOI: 10.1097/ALN.0000000000003254

<zdoi;. DOI: 10.1097/ALN.0000000000003254>

risk factor identification and modification has been the mainstay of management.

Over the last decade, there has been escalating interest in perioperative hemodynamic optimization in the context of noncardiac surgery, particularly in the exploration of perioperative hypotension as a potentially modifiable risk factor for AKI,[7,10] stroke,[11] myocardial injury,[12–15] and death.[16,17] Recent research supports an association of intraoperative hypotension with renal complications after noncardiac surgery. Specifically, Kidney Disease Improving Global Outcomes Stage I injury[14,15] was associated with mean arterial pressure (MAP) of less than 55 mmHg for 1 to 5 min,[3,13,14,18] less than 60 mmHg for greater than 10 min,[19] less than 65 mmHg for 10 to 20 min, or a relative decrease in MAP of greater than 20% from baseline value for 90 min or longer.[15]

In contrast, critical MAP thresholds and their association with AKI and renal replacement therapy have not been established in the context of cardiac surgery. As such, no guidelines are available for intraoperative MAP management during cardiopulmonary bypass (CPB), or before or after CPB.[12] To date, only one small perioperative study exists (n = 276) in this patient population, where MAP was specified as one of four "bundled" treatment variables to reduce the incidence of AKI in the ICU.[14] Additional limitations of available studies include their inability to account for minute-to-minute blood pressure variations,[20] and the fact that they were limited to blood pressure management either during CPB[21] or postoperatively in the ICU.[15] Thus, we sought to evaluate the association of intraoperative hypotension during all critical stages of cardiac surgery and *de novo* renal replacement therapy after surgery. We hypothesized that longer durations of hypotension during and post-CPB would be associated with new renal replacement therapy after cardiac surgery.

Materials and Methods

Design and Selection Criteria

This was a single-center retrospective study of 6,523 consecutive adult patients older than 18 yr of age, who underwent cardiac surgery requiring CPB at the University of Ottawa Heart Institute, Ottawa, Canada (a high-volume, university-based tertiary care hospital) between November 1, 2009, and April 30, 2015. Patients who were dialysis-dependent, received renal replacement therapy within 60 days before the index procedure, underwent thoracic aorta or off-pump procedures, cardiac transplantation, insertion of ventricular assist devices, or died before receiving renal replacement therapy, were excluded.

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Both the primary outcome and subgroup analyses, as well as the plan for statistical analysis, were made before accessing the data. The University of Ottawa Heart Institute Research Ethics Board approved this protocol and waived the need for individual patient consent.

Data Sources

We performed a retrospective analysis of prospectively collected data from the University of Ottawa Heart Institute perioperative database, which is a multimodular database managed by a multidisciplinary committee that undergoes regular, scheduled quality assurance audits. This database contains patient demographics, comorbidities, intraoperative management and hemodynamics, postoperative interventions, and in-hospital outcomes.[22]

All intraoperative invasive blood pressure measurements were recorded automatically every 15 s in an electronic patient record (CompuRecord, Philips Medical Systems, The Netherlands), with artifacts removed by an automated algorithm as previously described.[21,23] Briefly, the median MAP value for each minute was used in the analysis. Any aberrant (*i.e.*, isolated MAP value that differed more than 50% from both preceding and subsequent values) or absent MAP values were removed.[12,16] MAP readings were analyzed from the onset of end-tidal carbon dioxide (*i.e.*, induction) until the last reading (*i.e.*, the conclusion of anesthesia and transfer of patient from the operating room to the ICU).[12,16] MAP values from noninvasive blood pressure measurements were not included in this study. Intraoperative hemodynamic data were processed by using R (version 3.2.1; https://cran.rproject. org/bin/windows/base/old/3.2.1/; accessed June 1, 2015).

Outcomes

The primary outcome was new-onset postoperative renal replacement therapy during the index surgical admission. The decision to initiate renal replacement therapy was made by consensus of the consulting nephrologist, critical care physician, and cardiac surgeon. This decision was based primarily on rising creatinine values and oliguria as per the Kidney Disease Improving Global Outcomes criteria.[12,16] Secondary outcomes included stages of AKI as per Kidney Disease Improving Global Outcomes criteria: Kidney Disease Improving Global Outcomes Stage 1 (absolute increase in serum creatinine of 0.3 mg/dl or more or relative increase of 1.5- to 2-fold from the baseline value), and combined Stage 2 and cases of Stage 3 injury not requiring renal replacement therapy (relative increase in serum creatinine of twofold or more from baseline), occurring within 48 h of surgery.[12,16] We also examined the association between intraoperative hypotension and any AKI not requiring renal replacement therapy, as defined by the Kidney Disease Improving Global Outcomes criteria.

Exposure and Covariate Definitions

Similar to our previous study,[24] hypotension was defined by three *a priori* designated MAP thresholds of less than

55, 55 to 64, and 65 to 74 mmHg, before, during, and after CPB. These MAP thresholds were selected based on values shown to be associated with harm during cardiac and noncardiac surgery.[24–26] Cumulative durations of hypotension were assessed. The covariates used in this study and their definitions are listed in Supplemental Digital Content, table 1 (http://links.lww.com/ALN/C325).

Statistical Analysis

Continuous variables were visually inspected for normality using frequency histograms. Parametrically distributed variables were analyzed by using one-sided analysis of variance and presented as mean ± SD. Nonparametric variables were analyzed by using the Wilcoxon rank sum test and presented as median (interquartile range). Categorical variables were analyzed by using chi-square test and presented as number (proportion).

The possible association between hypotension and *de novo* renal replacement therapy was examined by using multivariable logistic regression with adjustment for prespecified renal replacement therapy risk factors, which were selected based on literature review (Supplemental Digital Content, table 2, http://links.lww.com/ALN/C324).[16] Three logistic regression models were constructed, each for a predefined MAP threshold. In each of these models, MAPs within or below that threshold before, during, and after CPB were each entered as an independent variable. For instance, for the multivariable model reported in figure 1, MAPs less than 55 mmHg before, during, and after CPB were entered as independent variables along with the prespecified renal replacement therapy risk factors. This modeling process was repeated for MAP between 55 and 64 mmHg, and for MAP between 65 and 74 mmHg. We tested for the presence of any interaction between MAP of less than 55 mmHg before, during, and after CPB and each of these covariates using multiplicative interaction terms. Specifically, we added one at a time into the multivariable logistic regression model, an interaction term of MAP less than 55 mmHg before CPB × each of the model covariates. We then repeated this process for covariate interaction with MAP less than 55 mmHg during and after CPB.

We conducted a *post hoc* analysis to examine the association between intraoperative hypotension and postoperative AKI of any severity, as defined by the Kidney Disease Improving Global Outcomes criteria. The same multivariable model was used to determine the association between intraoperative hypotension with different Kidney Disease Improving Global Outcomes stages of AKI.

The measure of association was demonstrated using odds ratio and associated 95% CI. We defined a minimum clinically meaningful effect as more than 1.05 per 10 min of hypotension, and more than 1.5 for other covariates. As three different MAP thresholds were tested, we used the Bonferroni method to correct for multiple testing, with statistical significance defined by a two-tailed $P < 0.017$. All analyses were conducted using SAS version 9.4 (SAS Institute, USA).

Missing Data

Main outcome and exposure variables were complete for all included subjects. The intraoperative fluid balance was imputed using the group mean for 341 (5.2%) patients. Left ventricular ejection fraction was imputed using the group mean for 101 (1.5%) patients. Weight and height were imputed with the group mean for 15 and 21 patients, respectively. The proportion of absent and artefactual MAP values removed was less than 1% of the total.

Results

Of the 6,523 patients included in this study, 336 (5.2%) underwent *de novo* postoperative renal replacement therapy. The absolute risk of renal replacement therapy was 2.3% (n = 64) in isolated coronary artery bypass graft (CABG), 2.4% (n = 27) in single valve, and 10.9% (n = 245) in combined valve(s) with or without CABG groups. The demographic and perioperative characteristics of patients with and without new postoperative renal replacement therapy are presented in table 1. The two groups were heterogenous at baseline, with known AKI risk factors more prevalent in patients who required postoperative renal replacement therapy.[3,12,16,27] Specifically, patients requiring *de novo* renal replacement therapy were more likely to have heart failure, peripheral arterial disease, chronic renal disease, anemia, and endocarditis, to present emergently for surgery with cardiogenic shock, to undergo complex procedures with prolonged CPB duration, to have lower nadir hematocrit on pump, to undergo intraoperative transfusion, to have a smaller net positive intraoperative fluid balance, to be more frequently supported by vasopressors and inotropes, and to have a higher incidence of new-onset postoperative atrial fibrillation.

Patients who underwent *de novo* renal replacement therapy had longer operative durations during and after CPB, as well as MAP less than 65 mmHg before, and MAP less than 75 mmHg in the CPB and post–CPB period (table 2). The absolute risk of new renal replacement therapy was higher with lower MAP thresholds in a dose-dependent manner. Notably, it was highest in those who were exposed to longer than average durations of MAP less than 55 mmHg at any time (table 2).

Table 3 illustrates the association between new renal replacement therapy and various thresholds of hypotension before, during, and after CPB. Renal replacement therapy was independently associated with sustained periods of MAP less than 65 mmHg after CPB. Specifically, each cumulative 10-min epoch of MAP less than 55 mmHg after CPB was associated with an adjusted odds ratio of 1.13 (95% CI, 1.05 to 1.23; $P = 0.002$); and each 10-min epoch of MAP between 55 and 64 mmHg after CPB was associated with an adjusted

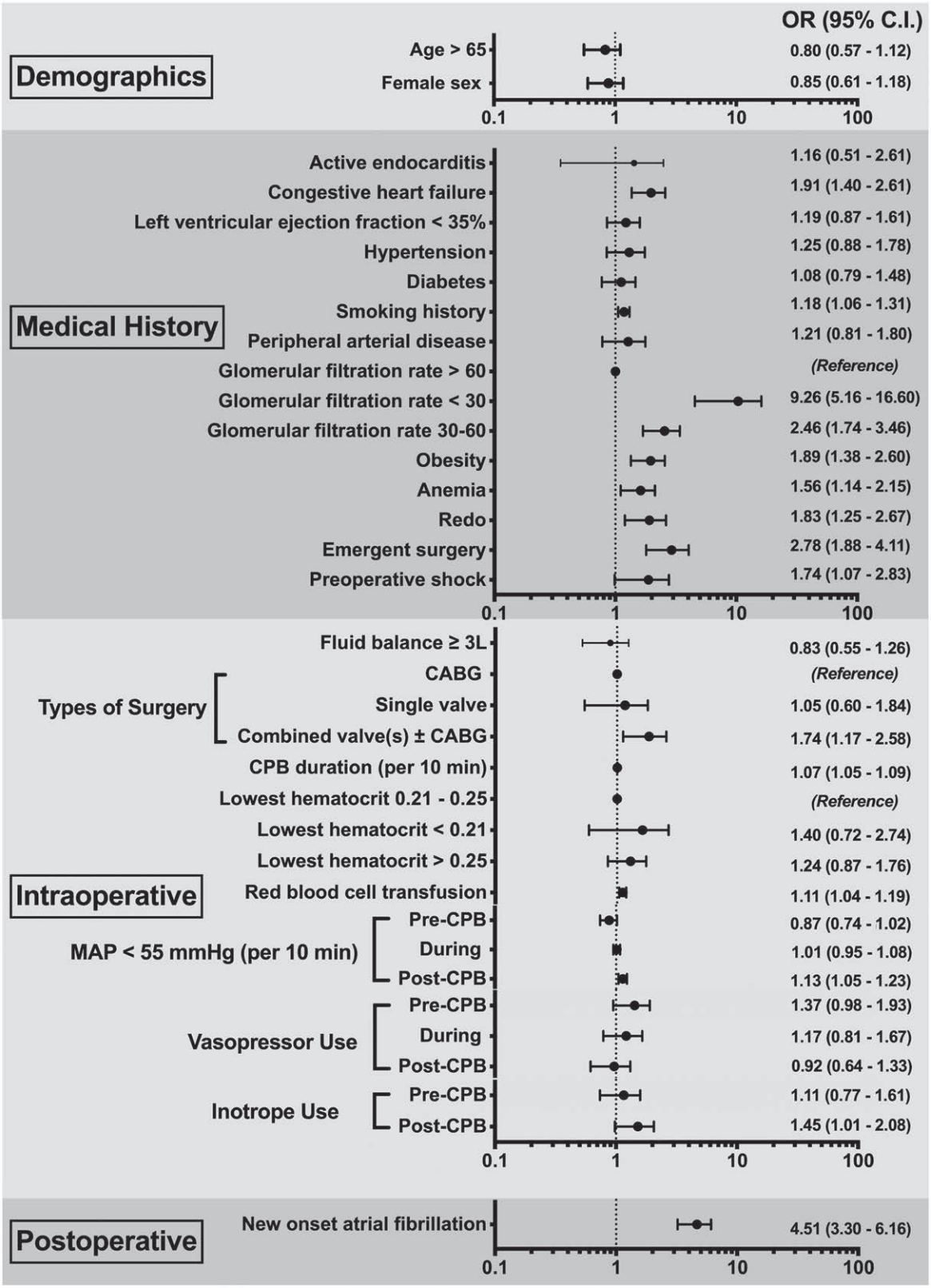

Fig. 1. Multivariable predictors of *de novo* postoperative renal replacement therapy. CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; OR, odds ratio; Redo, redo sternotomy.

Table 1. Characteristics of Patients with and without Postoperative Renal Replacement Therapy

Variable	Renal Replacement Therapy (n = 336)	No Renal Replacement Therapy (n = 6,187)	Std. Diff	*P* Value
Demographic				
Age, median (IQR), yr	68 (59 to 76)	67 (59 to 75)	0.002	0.501
Female sex, n (%)	103 (30.7)	1,720 (27.8)	0.063	0.256
Medical history, n (%)				
Hypertension	245 (72.9)	4,523 (73.1)	–0.004	0.940
LVEF < 35%	218 (64.9)	3,756 (60.7)	0.086	0.127
Heart failure	223 (67.0)	1,643 (26.6)	0.871	< 0.0001
Peripheral arterial disease	52 (15.5)	644 (10.4)	0.151	0.003
Smoking History				0.051
Never	111 (33.0)	2,296 (37.1)	–0.085	
Current	44 (13.1)	1,011 (16.3)	–0.092	
Former (quit < 30 d)	21 (6.3)	390 (6.3)	–0.002	
Former (quit > 30 d)	160 (47.6)	2,490 (40.3)	0.149	
GFR (ml/min per 1.73 m^2)				< 0.0001
> 60	159 (47.3)	4,757 (76.9)	–0.640	
30–60	139 (41.3)	1,327 (21.5)	0.439	
< 30	38 (11.3)	103 (1.7)	0.399	
Diabetes on medications	99 (29.5)	1,609 (26.0)	0.077	0.160
Obesity	117 (34.8)	2,056 (32.9)	0.034	0.547
Anemia	212 (63.1)	1,937 (31.3)	0.672	< 0.0001
Active endocarditis	21 (6.3)	94 (1.5)	0.247	< 0.0001
Emergent surgery	121 (36.0)	393 (6.4)	0.779	< 0.0001
Preoperative shock	71 (21.1)	152 (2.5)	0.605	< 0.0001
Reoperative procedure	84 (25.0)	442 (7.1)	0.501	< 0.0001
Intraoperative				
Type of surgery, n (%)				< 0.0001
CABG only	64 (19.1)	2,801 (45.3)	–0.585	
Single Valve	27 (8.0)	1,142 (18.5)	–0.311	
Combined valve(s) ± CABG	245 (72.9)	2,244 (36.3)	0.792	
Bypass duration, mean ± SD, min	165.6 ± 87.0	103.6 ± 49.9	0.016	< 0.0001
Lowest hematocrit on pump, n (%)				< 0.0001
< 0.21	22 (6.7)	104 (1.7)	0.247	
0.21–0.25	138 (42.2)	1,237 (20.2)	0.470	
> 0.25	167 (51.1)	4,783 (78.1)	–0.599	
Massive transfusion, n (%)	114 (33.9)	265 (4.3)	0.814	< 0.0001
Packed erythrocytes, median (IQR), units	2 (0 to 5)	0 (0 to 0)	0.000	< 0.0001
Vasopressor use pre-CPB	125 (37.2)	730 (11.8)	0.618	< 0.0001
Inotrope use pre-CPB	95 (28.3)	619 (10.0)	0.477	< 0.0001
Vasopressor use during CPB	215 (64.0)	1,600 (25.9)	0.830	< 0.0001
Inotrope use during CPB	190 (56.6)	1,144 (18.5)	0.855	< 0.0001
Vasopressor use post-CPB	245 (72.9)	2,371 (38.3)	0.743	< 0.0001
Inotrope use post-CPB	197 (58.6)	1,302 (21.0)	0.831	< 0.0001
Fluid balance, median (IQR), ml	550 (–1,884 to 2,065)	1,840 (980 to 2,600)	0.000	< 0.0001
Postoperative, n (%)				
New-onset atrial fibrillation	135 (40.2)	487 (7.9)	0.817	< 0.0001

Specific variable definitions are provided in Supplemental Digital Content, table 1 (http://links.lww.com/ALN/C325).

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; GFR, glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; Std. diff, standardized difference.

odds ratio of 1.12 (95% CI, 1.06 to 1.18; $P = 0.0001$) of new renal replacement therapy (Supplemental Digital Content, table 3, http://links.lww.com/ALN/C328).

Figure 1 illustrates the multivariable predictors of renal replacement therapy. The multivariable model was accurate (c-statistic = 0.92) and reliable (Hosmer–Lemeshow $P = 0.071$). On testing of multiplicative interaction terms, we found that pre–CPB MAP less than 55 mmHg amplified the effect of diabetes and procedural complexity on new renal replacement therapy; whereas the absence of MAP less than 55 mmHg during CPB amplified the effect of left ventricular ejection fraction less than 35% and erythrocyte transfusion on new renal replacement therapy; and the absence of MAP less than 55 mmHg after CPB amplified the effect of emergent procedure and hemodilution on new renal replacement therapy (Supplemental Digital Content, table 4, http://links.lww.com/ALN/C327).

The association of intraoperative hypotension with Kidney Disease Improving Global Outcomes Stage 1, and combined Stage 2 and 3 without renal replacement therapy,

Table 2. Mean Durations of Hypotension before, during, and after Cardiopulmonary Bypass and Their Corresponding Renal Replacement Therapy Risk

Timing		Duration (min)			Renal Replacement Therapy	
		Renal Replacement Therapy, Mean ± SD	No Renal Replacement Therapy, Mean ± SD	*P* Value	Absolute Risk, n (%)	*P* Value
Pre-CPB	Total Duration MAP (mmHg)	127 ± 46	122 ± 35	0.227	—	—
	< 55	6 ± 11	4 ± 7	0.001	96 (7)	0.0001
	55–64	17 ± 18	13 ± 14	< 0.0001	161 (6)	0.003
	65–74	29 ± 22	29 ± 19	0.545	202 (5)	< 0.0001
CPB	Total Duration MAP (mmHg)	190 ± 130	106 ± 56	< 0.0001	—	—
	< 55	23 ± 33	10 ± 16	< 0.0001	128 (12)	< 0.0001
	55–64	42 ± 34	256 ± 21	< 0.0001	193 (8)	< 0.0001
	65–74	37 ± 34	28 ± 20	< 0.0001	189 (6)	0.002
Post-CPB	Total Duration MAP (mmHg)	109 ± 60	76 ± 35	< 0.0001	—	—
	< 55	15 ± 32	4 ± 9	< 0.0001	108 (18)	< 0.0001
	55–64	36 ± 35	17 ± 16	< 0.0001	167 (101)	< 0.0001
	65–74	39 ± 33	29 ± 19	< 0.0001	191 (6)	0.0004

CPB, cardiopulmonary bypass; MAP, mean arterial pressure.

Table 3. Adjusted Odds Ratios of Postoperative Renal Replacement Therapy across Different Thresholds and Durations of Intraoperative Hypotension

MAP (mmHg) per 10 minutes	Adjusted OR (95% CI)	*P* Value
Pre-CPB		
< 55	0.87 (0.74–1.02)	0.077
55–64	0.98 (0.89–1.07)	0.603
65–74	0.97 (0.91–1.05)	0.479
During CPB		
< 55	1.01 (0.95–1.08)	0.653
55–64	1.06 (1.01–1.12)	0.032
65–74	1.04 (0.98–1.09)	0.219
Post-CPB		
< 55	1.13 (1.05–1.23)	0.002
55–64	1.12 (1.06–1.18)	0.0001
65–74	1.01 (0.96–1.07)	0.651

CPB, cardiopulmonary bypass; MAP, mean arterial pressure; OR, odds ratio.

is summarized in table 4. We also observed an increased odds of Kidney Disease Improving Global Outcomes Stage 2 and 3 AKI when MAP fell less than 65 mmHg after CPB. During the first 7 postoperative days, the median rise in creatinine from baseline was 156 μmol/l in renal replacement therapy patients and 9 μmol/l in non–renal replacement therapy patients.

In the *post hoc* analysis with *any* AKI as the outcome (Supplemental Digital Content, table 5, http://links.lww.com/ALN/C326), we found post–CPB hypotension to be associated with AKI in a dose-dependent fashion, such that each 10-min epoch of MAP less than 55 mmHg was associated with a 19% increase in the odds of AKI (adjusted odds ratio, 1.19; 95% CI, 1.10 to 1.30), and each 10-min epoch of MAP between 55 to 64 mmHg was associated with a 10% increase in the odds of AKI (adjusted odds ratio, 1.10; 95% CI, 1.06 to 1.14).

Discussion

In this single-center, retrospective study of adult patients who underwent cardiac surgery requiring CPB, the incidence of *de novo* renal replacement therapy was 5.2% (n = 336). We found an increased odds of *de novo* renal replacement therapy as well as AKI of any severity when MAP fell less than 65 mmHg after CPB, such that every 10 additional minutes of MAP between 55 and 64 mmHg after CPB increased the odds of renal replacement therapy by 12% (adjusted odds ratio, 1.12; 95% CI, 1.06 to 1.18; $P = 0.0001$), and every additional 10 min of MAP less than 55 mmHg increased the odds of renal replacement therapy by 13% (adjusted odds ratio, 1.13; 95% CI, 1.05 to 1.23). In addition, the odds of acute kidney injury of any severity increased by 19% when the post-CPB MAP fell less than 55 mmHg, and by 10% when post-CPB MAP fell between 55 and 64 mmHg. We did not observe an association between renal injury and hypotension before and during CPB.

This study is novel, as it explores the association between hypotension and *de novo* renal replacement therapy during physiologically distinct periods of cardiac surgery on a per-minute basis, by exploiting continuous high-fidelity intraoperative recording of invasive blood pressure measurements. Our findings are important especially in the absence of effective preventative measures for cardiac surgery-related AKI,[7,25,28–45] as they point to hypotension as a potentially modifiable risk factor for renal replacement therapy if appropriately treated to correct its underlying cause.

Table 4. Adjusted Odds Ratios of KDIGO Stage 1 and Combined Stage 2 and 3 Acute Kidney Injury across Different Thresholds and Durations of Intraoperative Hypotension

MAP (mmHg) per 10 minutes	KDIGO Stage 1		Combined KDIGO Stage 2 and 3	
	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Pre-CPB				
< 55	1.00 (0.90–1.12)	0.957	0.95 (0.81–1.13)	0.586
55–64	0.97 (0.91–1.03)	0.286	0.96 (0.86–1.07)	0.442
65–74	0.97 (0.93–1.02)	0.217	0.97 (0.89–1.06)	0.535
During CPB				
< 55	0.98 (0.93–1.03)	0.371	1.03 (0.96–1.10)	0.412
55–64	1.02 (0.98–1.06)	0.456	1.06 (0.99–1.13)	0.101
65–74	1.02 (0.98–1.06)	0.357	0.99 (0.92–1.05)	0.666
Post-CPB				
< 55	0.97 (0.90–1.04)	0.375	1.09 (1.02–1.16)	0.007
55–64	0.99 (0.95–1.04)	0.801	1.13 (1.06–1.20)	0.0001
65–74	1.025 (0.99–1.07)	0.179	1.02 (0.96–1.09)	0.483

CPB, cardiopulmonary bypass; KDIGO, Kidney Disease Improving Global Outcomes; MAP, mean arterial pressure; OR, odds ratio.

The potential benefits of maintaining normotension after cardiac surgery have previously been demonstrated by Magruder *et al.* in a small case-control study, where patients who developed AKI were matched to those who did not (n = 85 in each group).[23] In this study, the absolute risk of AKI was elevated in patients with sustained MAP less than 60 mmHg for 15 min or greater (70% *vs.* 42%, respectively; $P < 0.001$) during the first 48 postoperative hours.[35,46–48] Similarly, in the recent Prevention of Cardiac Surgery-associated AKI trial, where maintenance of MAP greater than 65 mmHg was one of four "Kidney Disease Improving Global Outcomes bundle" variables that formed the basis for the trial intervention, there was a reduction of the incidence of AKI in the MAP greater than 65 mmHg group as compared to controls (55.1% *vs.* 71.7%, absolute risk reduction, 16.6%; $P = 0.004$).[7] Our findings corroborate both of these studies, as well as our previous study of noncardiac surgery patients, where we observed an association between AKI and hypotension (specifically, MAP less than 55 mmHg for more than 10 min and MAP of less than 60 mmHg for 11 to 20 min) in a graded fashion.[23] Further prospective studies are warranted to confirm the MAP thresholds and durations identified in the current study and to determine whether goal-directed therapies targeting specific MAP ranges can serve to reduce this complication.

Of note, although the association between intraoperative hypotension and renal replacement therapy in the current study was statistically significant after multivariable adjustment, it was limited to more severe derangement during the post-CPB period and was weaker in comparison to some patient and procedure-related factors such as preexisting renal insufficiency, heart failure, obesity, complex or emergent surgery, and new-onset postoperative atrial fibrillation. Nonetheless, relative to the nonmodifiable nature of most of these risk factors, maintaining normotension during the post-CPB period is a more achievable goal.

We did not observe an association between pre-CPB hypotension and renal replacement therapy. However, we found that pre-CPB MAP less than 55 mmHg amplified the effect of diabetes and procedural complexity on new renal replacement therapy. This finding points to specific patient groups who may benefit the most from targeted hemodynamic interventions.

Despite CPB being a critical period for end-organ function and a known risk factor of AKI, we did not find an association between CPB hypotension and new renal replacement therapy or milder degrees of renal injury. Our findings are consistent with the literature. In a study of 122 patients randomly assigned into three groups by targeting MAPs of 45 to 59, 60 to 69, and 70 to 95 mmHg during CPB, Sirvinskas *et al.*[49] found no relationship between MAP management and subsequent renal dysfunction as defined by Risk, Injury, Failure, Loss of function, End stage renal disease (RIFLE) Stage 2 criteria within the first 3 postoperative days.[21] Similarly, in a retrospective analysis of 920 patients, Hasse *et al.* failed to demonstrate an association between MAP of less than 50, 60, or 70 mmHg and postoperative AKI as defined by RIFLE Stage 1 criteria within the first 7 postoperative days.[12] Despite the availability of continuously recorded MAP data, the lack of MAP artifact removal, and the lack of consideration for pre- and post-CPB hypotension were weaknesses of these studies.[49]

Our findings of other independent renal replacement therapy risk factors are consistent with the literature. These factors are heart failure,[50] peripheral arterial disease,[50] glomerular filtration rate less than 60 ml/min per 1.73 m^2,[32,41] obesity,[25,31,33] emergent surgery,[25,39,41] preoperative shock,[25,29,40] reoperative procedure,[7,33,39,41] complex surgery,[39] and perioperative transfusion.[28,30] Of these, CPB duration,[25,39,41] anemia,[37,39] and new-onset postoperative atrial fibrillation are potentially modifiable.[7,34] Interestingly,

MAP less than 55 mmHg during CPB was observed to amplify the effect of left ventricular ejection fraction less than 35%, erythrocyte transfusion, and new-onset postoperative atrial fibrillation on new renal replacement therapy. MAP less than 55 mmHg post-CPB was observed to amplify the effect of emergent procedure, preoperative cardiogenic shock, and hemodilution on new renal replacement therapy. These findings form the initial steps of identifying a subset of high-risk patients who may benefit from increased MAP thresholds during CPB and postoperatively.

It is important to recognize that in this study, the association between intraoperative hypotension and renal replacement therapy was not as strong in comparison other studied factors such as low baseline glomerular filtration rate, complexity and urgency of the surgery, and postoperative new-onset atrial fibrillation. Regardless, intraoperative hypotension was observed to intensify the effect of these factors on *de novo* acute kidney injury after cardiac surgery. This indicates the complexity of the association between intraoperative hypotension and acute kidney injury, with many factors that need to be taken into consideration. Moreover, most of these risk factors are nonmodifiable, while maintaining normotension intraoperatively is a relatively achievable goal.

Limitations

Our study has several limitations. First, this is a single-center study. Further reports from other healthcare jurisdictions are warranted to verify the generalizability of our findings. Second, we are unable to infer causality from an observational design, which, despite careful risk adjustment, is subject to unmeasured confounding. Further prospective studies are needed to determine whether renal replacement therapy results directly from hypotension or indirectly through associated factors, such as low cardiac output syndrome, decreased renal blood flow, chronic obstructive pulmonary disease, hypovolemia, or the management of these factors. Third, in this exploratory analysis, we sought to identify the absolute hypotension thresholds in association with renal replacement therapy. This approach does not account for the possible rightward renal autoregulatory shift that occurs in patients with chronic hypertension. Fourth, no analyses were performed on the effects of relative hypotension with respect to a patient's normal baseline blood pressure, which may limit the generalizability of our findings. Additionally, the patients who died before the initiation of renal replacement therapy were excluded, and this may have led to a biased event estimate. Finally, this study did not explore directly whether treatment of intraoperative hypotension would improve postoperative renal outcomes.

Conclusions

In conclusion, we observed an increased risk of *de novo* postoperative renal replacement therapy when MAP fell less than 65 mmHg for more than 10 min after CPB. Specifically, we found that for each 10-min epoch of MAP less than 55 mmHg post-CPB there was a 13% increased odds of new renal replacement therapy and 19% increased odds of any AKI, while each 10-min epoch between 55 and 64 mmHg was associated with a 12% increased odds of new renal replacement therapy and 10% increased odds of any AKI. These findings possibly highlight the importance of post-CPB MAP management as a potentially modifiable factor in the prevention of renal replacement therapy. Further studies are needed to confirm the generalizability of our findings in different practice settings, as well as to evaluate the effect of goal-directed hemodynamic management strategies in cardiac surgery patients.

Research Support

Supported in part by the Research Funds of the Division of Cardiac Anesthesiology of the University of Ottawa Heart Institute, Ottawa, Canada. Dr. Chung was supported by a Summer Studentship Award from the Heart and Stroke Foundation (Ontario, Canada) Hannah Pherril Scholarship to conduct research during the summer of 2015. Dr. Sun is supported by the Ottawa Heart Institute Research Corporation.

Competing Interests

Dr. Ruel is supported by Medtronic (research grant; Brampton, Canada) and Cryolife (steering committee, PROACT Xa; Kennesaw, Georgia). Dr. Sun served on the advisory board for Edwards Lifesciences (Mississauga, Canada). The other authors declare no competing interests.

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