Journal of Cardiothoracic and Vascular Anesthesia 31 (2017) 522–528

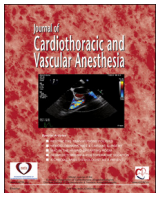
HOSTED BY

ELSEVIER

Contents lists available at ScienceDirect

ScienceDirect

journal homepage: www.jcvaonline.com



Impact of Intraoperative Hypotension During Cardiopulmonary Bypass on Acute Kidney Injury After Coronary Artery Bypass Grafting

Thijs C.D. Rettig, MD[*], Linda M. Peelen, PhD[†,‡], Guillaume S.C. Geuzebroek, MD, PhD[§], Wilton A. van Klei, MD, PhD[†], Christa Boer, PhD[¶], Jan Willem van der Veer, MD[*], Jan Hofland, MD, PhD[#], Ewoudt M.W. van de Garde, PharmD, PhD[**], Peter G. Noordzij, MD, PhD[*,1]

[*]*Department of Anesthesiology, Intensive Care, and Pain Medicine, St. Antonius Hospital, Nieuwegein, Netherlands*
[†]*Department of Anesthesiology, Intensive Care, and Emergency Medicine, University Medical Center Utrecht, Utrecht, Netherlands*
[‡]*Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands*
[§]*Department of Cardiothoracic Surgery, Radboud University, Nijmegen, Netherlands*
[¶]*Department of Anesthesiology, Vrije Universiteit University Medical Center, Amsterdam, Netherlands*
[#]*Department of Anesthesiology, Radboud University, Nijmegen, Netherlands*
[**]*Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, Netherlands*

Objective: The aim of this study was to investigate whether acute kidney injury (AKI) after coronary artery bypass grafting can be attributed to intraoperative hypotension during cardiopulmonary bypass (IOH-CPB).
Design: Retrospective analysis.
Setting: Tertiary-care hospital.
Participants: Patients undergoing on-pump coronary artery bypass grafting from June 2011 to January 2014.
Interventions: None.
Measurements and Main Results: IOH-CPB was defined as blood pressure below several absolute and relative mean arterial pressure (MAP) thresholds and as the area under the curve for absolute MAP thresholds. AKI was defined as an absolute increase in serum creatinine of ≥ 26 μmol/L within 48 hours or an increase to 150% or more within 7 days of surgery. Poisson regression with robust standard errors both before and after adjustment for confounders was used. Of the 1,891 patients included, 386 (20%) developed AKI. In univariable analysis, all IOH-CPB thresholds defined as a MAP of 50 mmHg or less and as a decrease in MAP of 60% from baseline were associated with a 1.07-to-1.11 times increased risk of AKI per 10 minutes of IOH-CPB ($p < 0.01$). After adjustment for potential confounders, IOH-CPB, irrespective of the definition chosen, was not associated with an increased risk of AKI.
Conclusions: In the authors' study population, univariable analysis showed an association of IOH-CPB with AKI in patients undergoing isolated CABG, but this relationship disappeared after correction for well-known risk factors for AKI.
© 2017 Elsevier Inc. All rights reserved.

Key Words: acute kidney injury; hypotension; coronary artery bypass grafting; outcome

EACH YEAR, more than 1 million coronary artery bypass graft (CABG) procedures are performed in Europe and the United States alone.[1] A major determinant of outcome after

[1]*Address reprint requests to* Peter Noordzij, MD, PhD, Department of Anesthesiology, Intensive Care, and Pain Medicine, Koekoekslaan 1,3430 EM, Nieuwegein, Netherlands.
E-mail address: p.noordzij@antoniusziekenhuis.nl (P.G. Noordzij).

http://dx.doi.org/10.1053/j.jvca.2016.07.040
1053-0770/© 2017 Elsevier Inc. All rights reserved.

CABG is the development of postoperative acute kidney injury (AKI), which occurs in up to 30% of patients.[2,3] A recently published report showed that the occurrence of AKI after cardiac surgery increased in the past decade.[4] Although this effect is at least partially explained by better coding practices, these data also indicated that the pathophysiologic mechanisms of AKI after cardiac surgery still are not understood fully, which hampers development and use of preventive or treatment strategies.

The use of cardiopulmonary bypass (CPB) is a well-recognized cause of AKI after cardiac surgery.[5] Exposure of blood to the CPB circuit and surgical trauma itself induce a systemic inflammatory response and may lead to a reduced glomerular filtration rate through, for example, glomerular fibrin deposition.[6] Also, oxygen delivery to the renal medulla may be compromised by severe hemodilution during CPB.[7] The role of intraoperative hypotension during CPB (IOH-CPB) in the development of postoperative AKI is unclear.

A randomized, controlled trial in 300 patients undergoing cardiac surgery compared a mean arterial pressure (MAP) of 75 mmHg to 85 mmHg with 50 mmHg to 60 mmHg during CPB and reported similar AKI rates in both groups.[8] In a comparable study performed in the early 1990s, 248 patients randomized to an MAP of 80 mmHg to 100 mmHg during CPB seemed to have fewer cardiac and neurologic complications compared to patients randomized to an MAP of 50 mmHg to 60 mmHg, but the incidence of AKI was not assessed.[9] From these few studies, with a limited number of patients, it cannot be concluded whether IOH-CPB is involved in the pathophysiology of AKI after cardiac surgery.[10] In addition, the MAP targeted in these studies was higher than in daily practice, and, other than absolute IOH thresholds such as a decrease in MAP from baseline or the area under the curve (AUC), IOH below thresholds were not investigated. The aim of this study was to determine whether IOH-CPB was associated with the development of AKI using various definitions of IOH-CPB in a large cohort of patients undergoing CABG.

Methods

Study Population and Design

All patients who underwent a CABG procedure from June 2011 until January 2014 in the St. Antonius Hospital, Nieuwegein, Netherlands, with an available serum creatinine within 7 days prior to surgery and at least 1 available serum creatinine within 7 days after surgery, were eligible for inclusion in this observational retrospective study. Exclusion criteria were renal replacement therapy prior to surgery, unavailable perioperative blood pressure values, off-pump or concomitant open-chamber surgery, and postoperative extracorporeal membrane oxygenation.

The local Medical Research Ethics Committee approved the study and waived the need for informed consent (Research and Development Department, St. Antonius Hospital, trial number W15.024).

Anesthetic and Surgical Management

Routine perioperative care included induction of anesthesia with propofol, midazolam, fentanyl, and pancuronium and maintenance of anesthesia with propofol and fentanyl or remifentanil. All patients received antimicrobial prophylaxis (cefazolin) at induction of anesthesia followed by additional cefazolin every 4 hours for the duration of surgery. After sternotomy, heparin was administered intravenously and, at the end of surgery, neutralized by protamine. For CPB, nonpulsatile perfusion was used, with a flow of 2.0-to-2.4 L/min/m^2. After aortic cross-clamping, cardiac arrest was initiated using a cold crystalloid (Bleese, Fesenius Kabi, Bad Homburg, Germany) or blood (in case of minimal extracorporeal circulation) cardioplegic solution. Patients were cooled to a nasopharyngeal temperature of 32°C to 35°C. Before separation from CPB, patients were rewarmed to a nasopharyngeal temperature of at least 35.5°C.

Intraoperative management targeted a hematocrit of 22% and an S_VO_2 of 65%. The MAP during CPB was left to the discretion of the attending anesthesiologist and was dependent on the medical history (eg, hypertension, stroke). In general, an MAP of 45-to-50 mmHg was targeted during CPB. Red blood cell transfusion trigger was a hematocrit of 20% during CPB and a hematocrit of 25% after separation from CPB. After the surgical procedure, all patients were admitted to the intensive care unit for at least 24 hours.

Acute Kidney Injury

Serum creatinine was measured routinely as part of standard postoperative laboratory tests on postoperative days 1, 2, and 5. In some patients, additional creatinine measurements were available if ordered by the treating physician, and these also were included in the authors' analyses. Creatinine analysis was performed with the use of an enzymatic method on an automated platform (Roche Diagnostics, Mannheim, Germany).

The primary outcome was development of postoperative AKI, which was defined according to the 2011 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury as an absolute increase in serum creatinine of ≥ 26 μmol/L within 48 hours or an increase in serum creatinine to 150% or more within 7 days.[11]

Blood Pressure and IOH-CPB

Preoperatively, blood pressure was measured using the Omron M6 (Omron HEM-737 Intellisense, Omron Healthcare Inc., Lake Forest, IL) at the outpatient preanesthesia evaluation clinic. Blood pressure was measured in the sitting position with the cuff on the upper arm. The MAP resulting from this measurement served as the baseline MAP used in clinical practice and in the authors' analyses.

During surgery, the MAP was monitored invasively and recorded every minute in the electronic medical record system (MetaVision Suite, *i*MD*soft*, Dedham, MA). IOH-CPB was defined according to several absolute and relative MAP

threshold values. The authors calculated the time spent below absolute ($<40, <45, <50, <55, <60$, and <65 mmHg) and relative MAP thresholds ($>35\%, >40\%, >45\%, >50\%, >55\%$, and $>60\%$ decrease from baseline) in each patient. In addition, the authors calculated the AUC for absolute MAP threshold values ($<40, <45, <50, <55, <60$, and <65 mmHg). The AUC was defined as the sum of each blood pressure (MAP threshold value − MAP measured) multiplied by time (minutes) spent under the MAP threshold value.

Data Collection and Confounder Selection

Medical history and preoperative drug therapy were registered at the outpatient preanesthesia evaluation clinic. Intraoperative and postoperative data were collected routinely in the electronic medical record system. Potential confounders for the association of IOH-CPB and postoperative AKI were selected based on previous literature and biologic plausibility and included age, sex, diabetes (+type), hypertension, left ventricular ejection fraction, preoperative hemoglobin, preoperative creatinine, EuroSCORE, critical preoperative state (defined as ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the operating room, preoperative inotropic support, or intra-aortic balloon counterpulsation), allogeneic red blood cell (RBC) transfusion during surgery, autologous RBC transfusion during surgery, and duration of CPB.[12,13]

Missing Data

Omitting patients with missing data from the analyses (so-called complete case analysis) can result in biased effect estimates, as missing data typically do not occur completely at random but are associated with patient characteristics. To overcome this problem, the authors conducted multiple imputation analysis, a well-accepted statistical technique, to model the values that were missing and incorporate these into the analyses in the appropriate way. The authors used 10 imputation sets; analyses were conducted in each of the imputation sets, resulting estimates from each of these sets were pooled, and adjusted standard errors were calculated using Rubin's rule.[14–16]

Statistical Analysis

Baseline and perioperative characteristics were compared for patients with and without AKI. Continuous data are presented as mean and standard deviation or median and interquartile range (IQR) for normally and non-normally distributed data. Categorical data are described as numbers and percentages. The Student's t-test and the Mann-Whitney U-test were used to compare independent continuous variables between a patient with and without AKI for normally and non-normally distributed variables, respectively. The Fisher's exact test and the Pearson chi-squared test were used to compare categorical variables between patients with and without AKI when appropriate.

Subsequently, the authors assessed the association between IOH-CPB and AKI using regression analysis. They conducted Poisson regression analysis with robust standard errors and present resulting effect estimates as risk ratios with accompanying confidence intervals.[17] These analyses were conducted using only IOH-CB within the models (crude estimate) and after adjustment for the aforementioned potential confounders. The authors included IOH-CPB in the analyses as a continuous variable. To assess potential non-linearity of the association between IOH-CPB and AKI, the authors investigated models in which duration of IOH-CPB was included as a continuous variable, and after square root or log transformation, and compared their model fit based on log likelihood of the model. All analyses were repeated for all aforementioned IOH-CPB thresholds. To adjust for multiple testing, the authors used a more stringent level of significance of $p<0.01$ and hence present effect estimates with 99% confidence intervals. For statistical analysis, IBM SPSS version 22 was used.

Results

During the study period, 1,983 patients were eligible for analysis. After the exclusion of patients requiring renal replacement therapy prior to surgery (n = 10), patients who underwent off-pump or concomitant open-chamber surgery (n = 47), patients without an available preoperative or without at least 1 available postoperative creatinine (n = 24), and patients without perioperative blood pressure values available (n = 13), the final study population consisted of 1,891 patients (95%).

The mean age was 67 years, and 79% of the patients were male (Table 1). The most common comorbidities were hypertension (60%), diabetes (25%), and prior myocardial infarction (25%). Almost a quarter of the patients had a reduced left ventricular ejection fraction. The average baseline MAP was 98 ± 13 mmHg, and the mean baseline creatinine was 88 ± 24 μmol/L. During CPB, the average MAP was 55 ± 9 mmHg. The median EuroSCORE was 3 (IQR, 2-5), and 151 patients (8%) underwent an emergency procedure (Table 2). The mean durations of CPB and aortic cross-clamping were 89 ± 39 and 57 ± 27 minutes, respectively. Two hundred thirty-three patients (12%) received intraoperative allogeneic RBC transfusion. Baseline and perioperative characteristics according to complete and incomplete cases are shown in Supplementary Tables 1 and 2.

The times spent below the investigated IOH-CPB thresholds studied are presented in Table 3. All but 37 patients (2%) experienced IOH-CPB defined as an MAP below 50 mmHg with a median duration of 28 minutes (IQR, 13-47). The median duration of IOH-CPB defined as a decrease in MAP of 60% from baseline was 6 minutes (IQR, 1-16).

After surgery, 386 patients (20%) suffered from AKI, and 8 patients (0.4%) required renal replacement therapy due to kidney failure. The median length of hospital stay was 7 (IQR,

Table 1
Baseline Characteristics

Variable	All (N = 1,891)	AKI (n = 386)	No AKI (n = 1,505)	p Value	Incomplete
Male sex (n [%])	1,488 (78.7)	296 (76.7)	1,192 (79.2)	0.281	0
Age (yr)	67 ± 10	70 ± 9	66 ± 10	< 0.001	0
BMI (kg/m^2 [%])	27.6 ± 4.4	28.4 ± 4.8	27.3 ± 4.3	< 0.001	0
Comorbidity					
COPD (n [%])	134 (7.1)	40 (10.4)	94 (6.2)	0.005	0
Diabetes (n [%])					0
Insulin dependent	153 (8.1)	51 (13.2)	102 (6.8)	< 0.001	
Non-insulin dependent	317 (16.8)	86 (22.3)	231 (15.3)		
Hypertension (n [%])	1,136 (60.1)	265 (68.7)	871 (57.9)	< 0.001	0
Congestive heart failure (n [%])	29 (1.5)	14 (3.6)	15 (1.0)	< 0.001	0
Myocardial infarction (n [%])	466 (24.6)	107 (27.7)	359 (23.9)	0.116	0
Peripheral artery disease (n [%])	184 (10.0)	64 (16.9)	120 (8.2)	< 0.001	42 (2.2)
Previous stroke (n [%])	72 (3.8)	24 (6.2)	48 (3.2)	0.006	0
Previous cardiac surgery (n [%])	54 (2.9)	18 (4.8)	36 (2.4)	0.017	42 (2.2)
Pulmonary hypertension (n [%])	3 (0.2)	2 (0.5)	1 (0.1)	0.108	42 (2.2)
LVEF (n [%])					2 (0.1)
> 50%	1,462 (77.4)	263 (68.3)	1,199 (79.7)	< 0.001	
> 30% and ≤ 50%	368 (19.5)	95 (24.7)	273 (18.2)		
≤ 30%	59 (3.1)	27 (7.0)	32 (2.1)		
Baseline MAP (mmHg)	98 ± 13	98 ± 14	98 ± 13	0.977	412 (21.8)
Laboratory values					
Preoperative creatinine (μmol/L)	88 ± 24	103 ± 34	84 ± 19	< 0.001	0
Preoperative hemoglobin (mmol/L)	8.5 ± 0.9	8.1 ± 1.0	8.6 ± 0.8	< 0.001	130 (6.9)

NOTE. Values are mean (standard deviation) or absolute number (percentage). Student's t-test was used to test for the association of continuous variables and AKI. The Fisher's exact test and the Pearson chi-squared test were used to test for the association of categorical variables and AKI when appropriate.
Abbreviations: AKI, acute kidney injury; BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure.

5-10) and 5 (IQR, 3-6) days in patients with and without AKI, respectively ($p < 0.001$). In-hospital mortality was 3.1% in patients with AKI and 0.4% in patients without AKI ($p < 0.001$).

The association between IOH-CPB and AKI is presented in Figure 1. As transformation of duration of IOH-CPB did not improve model fit, the authors included the duration of IOH-CPB expressed in minutes in all subsequent models. In univariable analysis, the risk of AKI increased when the duration of IOH-CPB increased for absolute and relative IOH-CPB thresholds (Figs 1A and 1B) or when the AUC for IOH-CPB thresholds increased (Fig 1C), and this was more pronounced for the lowest IOH-CPB thresholds. For example, for IOH-CPB defined as an MAP of 65 mmHg, the risk of AKI increased by 1.004 (99% confidence interval [CI]:1.000-1.007) per minute below this threshold, and the risk increased to 1.011 (99% CI: 1.005-1.017) per minute for IOH-CPB defined as an MAP of 40 mmHg. This means that a patient who has an

Table 2
Perioperative Characteristics

Variable	All (N = 1,891)	AKI (n = 386)	No AKI (n = 1,505)	p Value	Incomplete
Operative					
Emergency procedure (n [%])	151 (8.2)	46 (12.2)	105 (7.1)	0.001	42 (2.2)
Critical preoperative state (n [%])	49 (2.7)	24 (6.3)	25 (1.7)	< 0.001	42 (2.2)
EuroSCORE	3 (2-5)	5 (3-7)	3 (1-5)	< 0.001	42 (2.2)
Duration of CPB (min)	89 ± 39	95 ± 64	87 ± 29	0.028	0
Duration of aortic cross-clamping (min)	57 ± 27	58 ± 23	57 ± 28	0.838	215 (11.4)
Average MAP during CPB (mmHg)	55 ± 9	55 ± 11	56 ± 9	0.046	0
Intraoperative RBC transfusion (n [%])	233 (12.3)	95 (24.6)	138 (9.2)	< 0.001	0
Outcome					
Resternotomy (n [%])	71 (3.8)	33 (8.5)	38 (2.5)	< 0.001	0
Length of stay (days)	5 (4-7)	7 (5-10)	5 (3-6)	< 0.001	14 (0.7)
In-hospital mortality (n [%])	18 (1.0)	12 (3.1)	6 (0.4)	< 0.001	10 (0.5)

NOTE. Values are mean (standard deviation), median (interquartile range), or absolute number (percentage). Student's t-test and the Mann-Whitney U-test were used to test for the association of normally and non-normally distributed continuous variables and AKI. The Fisher's exact test and the Pearson chi-squared test were used to test for the association of categorical variables and AKI when appropriate.
Abbrevaitions: AKI, acute kidney injury; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; RBC, transfusion, red blood cell transfusion.

Table 3
Time (minutes) Spent Under Absolute and Relative MAP Thresholds According to the Occurrence of AKI

Threshold	No AKI	AKI	p Value
Absolute (mmHg)			
< 65	63 (42-83)	68 (47-88)	0.009
< 60	53 (31-74)	60 (37-80)	< 0.001
< 55	40 (21-61)	47 (26-70)	< 0.001
< 50	26 (13-46)	34 (16-54)	< 0.001
< 45	15 (6-29)	19 (8-35)	< 0.001
< 40	7 (2-14)	8 (3-17)	0.004
Decrease from baseline (%)			
< 35	58 (36-81)	65 (43-86)	0.005
< 40	48 (26-73)	54 (32-77)	0.010
< 45	35 (17-60)	41 (23-66)	0.005
< 50	23 (9-45)	26 (11-53)	0.016
< 55	12 (4-29)	15 (6-34	0.055
< 60	5 (1-15)	6 (2-17)	0.043

Note. Values are median and interquartile range.
Abbreviations: MAP, mean arterial pressure.

MAP below 40 mmHg for 10 minutes has a $1.011^{10} = 1.12$ times higher risk of developing AKI postoperatively when compared to a patient whose MAP stays above 40 mmHg. After accounting for potential confounders, none of the IOH-CPB thresholds was associated with AKI (Fig 1D-1F).

Discussion

In this study including 1,891 patients undergoing on-pump CABG, the incidence of postoperative AKI was 20%, and 0.4% of patients required renal replacement therapy. IOH-CPB was not associated with an increased risk of postoperative AKI.

Previous studies have shown that AKI or even a slight increase of serum creatinine that did not meet the AKI criteria was associated with morbidity and mortality after surgery.[18] Whether postoperative AKI results from IOH-CPB is a matter of debate. Recently, several large retrospective analyses have addressed this topic in noncardiac surgery, and most of the studies carried out pointed to an association between IOH and AKI. For example, Walsh et al showed that a short duration of IOH defined as an MAP of 55 mmHg increased the risk of AKI after noncardiac, non-neurologic surgery, and Sun et al reported similar findings in a smaller but more detailed investigation.[19,20] The question is to what extent these results can be extrapolated from noncardiac surgery to cardiac surgery.

The authors performed a large retrospective analysis in patients undergoing on-pump CABG in whom preoperative and postoperative serum creatinine was measured routinely. The authors' results did not show an association between IOH-CPB and AKI. This was in accordance with the results of Azau et al,[8] who randomized 300 patients undergoing elective cardiac surgery to an MAP during CPB of 50 mmHg to 60 mmHg versus 75 mmHg to 85 mmHg. They found no association with postoperative AKI despite investigating different definitions for AKI. Haase et al retrospectively investigated 920 patients undergoing on-pump cardiac surgery.[21] Twenty percent of the patients developed AKI, and this was not dependent on IOH-CPB. The combination of severe hypotension (> 75th percentile of the AUC for MAP 50 mmHg) and severe anemia (< 25th percentile of the lowest hemoglobin) did yield an increased risk of AKI (adjusted odds ratio 3.4, 95% CI: 1.3-8.4, p = 0.010). Interestingly, in another retrospective study that included patients undergoing CABG and valve surgery, the incidence of AKI was 36%, and this was not dependent on IOH-CPB or the combination of IOH-CPB and anemia.[22]

Rather than studying IOH-CPB, defined as an absolute MAP threshold as in the previous studies, Kanji et al investigated a relative decrease in MAP in 157 patients undergoing on-pump cardiac surgery at high risk for developing AKI.[23] Forty-one percent of the patients developed AKI, and the occurrence of IOH-CPB defined as an arbitrarily chosen decrease in MAP of 26% from baseline was independently associated with AKI (odds ratio 2.8, 95% CI: 1.3-6.1, p = 0.009). The smallest relative decrease in MAP that the authors studied was 35% and yielded a risk ratio of 1.001 (99% CI: 0.997-1.006, p = 0.455) per minute below this threshold for the development of AKI. Also, IOH-CPB defined as relative decreases greater than 35% were not associated with AKI. It is possible that patients at high risk for postoperative AKI as in the study of Kanji et al are more susceptible to IOH-CPB than patients at normal risk as in the authors' population.

If IOH is indeed associated with AKI after noncardiac surgery, why is this relation not observed in on-pump cardiac surgery? A possible explanation may be that IOH during noncardiac surgery often is the result of a low-cardiac-output state caused by general anesthesia and a potential sign of reduced organ oxygen delivery; while in on-pump cardiac surgery, cardiac output and organ oxygen delivery are maintained by CPB. In an experimental study in pigs, increasing the pump flow rate increased visceral organ perfusion, while increasing the MAP with phenylephrine did not, suggesting that for preserving renal oxygen delivery, the focus should be on cardiac output and, to a lesser extent, IOH-CPB.[24] Another animal study showed that the mixed venous oxygen saturation, a sensitive marker for organ hypoperfusion, did not decline during normothermic CPB until pump flow rate was reduced to less than 2 L/min/m^2 despite a decrease in MAP from 71 mmHg to 56 mmHg.[25]

In the authors' study, the average MAP during CPB was 55 mmHg, and 95.2% of patients experienced IOH-CPB defined as an MAP below 45 mmHg with a median duration of 16 minutes. Compared to the MAP during CPB in other studies, this was rather low.[8,22] For example, in the study by Azau, the average MAP during CPB was 60 mmHg in the group randomized to an MAP of 50 to 60 and 79 mmHg in the group randomized to an MAP of 75 to 85. In the study by Haase et al, the median MAP during CPB was 68 (IQR, 64-73). Interestingly, despite this difference, the incidence of AKI was comparable among the studies (17% in the study by Azau et al, 20% in the study by Haase et al, and 20% in the authors' study).

Among the strengths of the authors' study was the large sample size of 1,891 patients undergoing on-pump CABG and

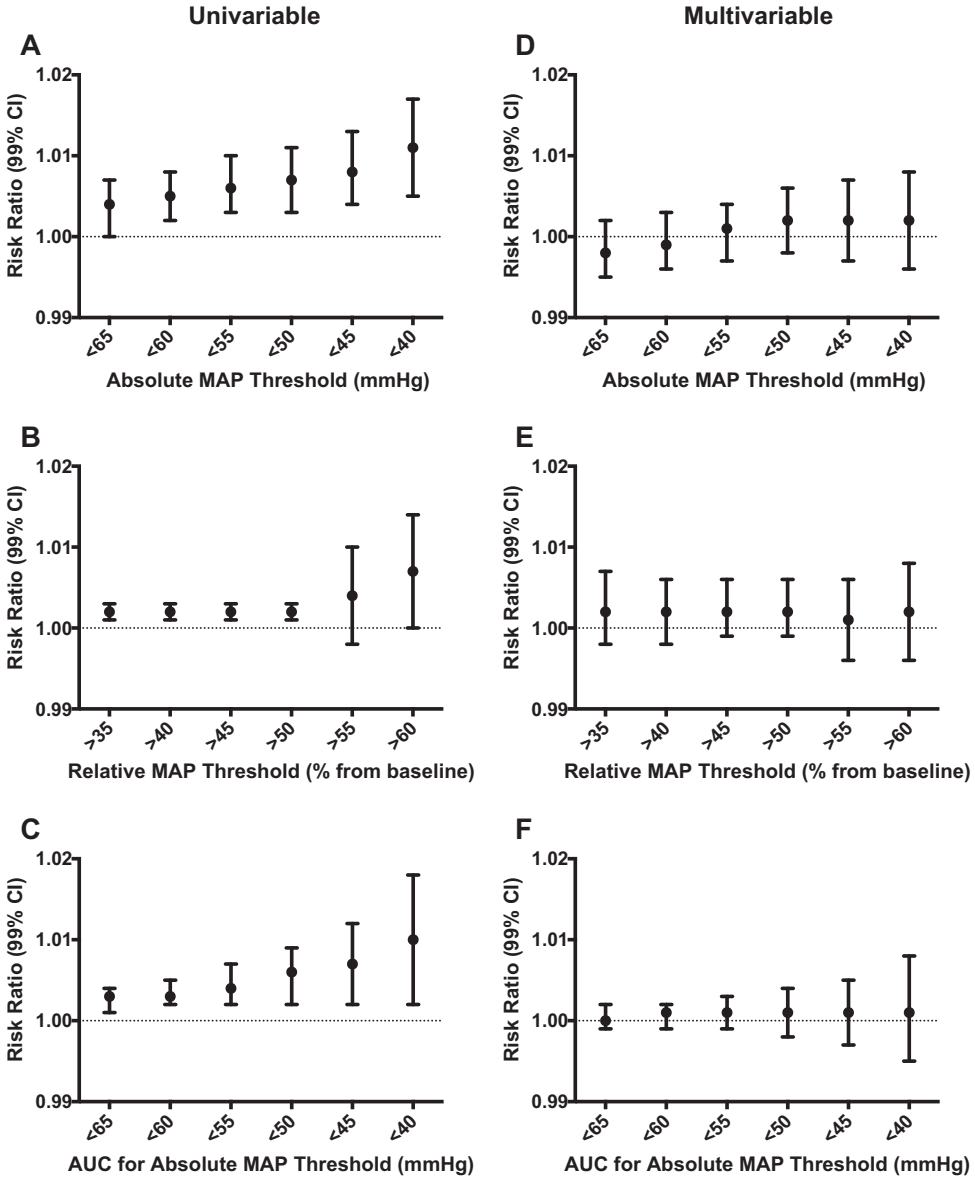


Fig 1. Univariable and multivariable analysis of absolute and relative mean arterial pressure (MAP) threshold values and area under the curve for MAP thresholds and acute kidney injury.

the use of multiple imputation to deal with missing values. As a result, the number of patients developing AKI was large, which enabled the authors to adjust for many confounders in the multivariable analysis. Also, the authors investigated multiple IOH-CPB threshold values (absolute, relative, and the AUC) ranging in severity from mild to severe. Finally, the authors corrected for multiple testing using a level of significance of $p < 0.01$, minimizing the risk of a false-positive finding (type-1 error).

Several limitations have to be addressed. First, this was a retrospective observational study, and the limitations of this design must be considered. For example, serum creatinine was not measured on each postoperative day, and information regarding postoperative urine output was unavailable. As a result, the incidence of AKI may have been underestimated. It also was possible that additional serum creatinine measurements outside the standard postoperative laboratory tests were ordered mainly in patients at high risk of AKI. If the targeted MAP during CPB in these patients was increased in an attempt to prevent AKI, a possible effect of IOH-CPB on AKI may have been dampened (so-called confounding by contraindication). Another limitation of the design of the authors' study is the fact that many factors influence the risk of AKI after on-pump CABG. Although they adjusted for a large number of potential confounders, they could not exclude the possibility of residual confounding. In that regard, the study design the authors used may be less suitable for studying IOH-CPB as a single phenomenon in the development of AKI after CABG. Also, as occurs in nonrandomized studies, treatment of IOH may have influenced the association between IOH-CPB and AKI. For example, the risk of AKI in a patient with an MAP of 50 mmHg while on vasopressor therapy may be different from a patient with an MAP of 50 mmHg without treatment; while in the authors' analyses, both situations were considered

similar. Second, IOH-CPB occurred in the vast majority of patients, making it hard to distinguish patients with and without IOH-CPB for some thresholds. Third, the authors could comment only on the association between IOH-CPB and AKI for the IOH-CPB thresholds analyzed. Fourth, the authors studied the relation between AKI and the MAP during CPB and not the MAP before or after the institution of CPB. Patients with IOH-CPB may have experienced IOH before and after the use of CPB (eg, due to a low hematocrit), and for patients without IOH-CPB, the opposite may have been true. In theory, this may have overestimated the effect of IOH-CPB on AKI. Fifth, the authors' results can be interpreted only in the context of AKI. They were not able to draw inferences on the association between IOH-CPB and other complications such as stroke.

Altogether, in this large cohort of patients undergoing CABG, the authors did not observe an association between IOH-CPB and AKI when they corrected this association for well-known confounders. Given the observational design of their study, they could not draw firm conclusions on the potential causal association between IOH-CPB and AKI. To this end, future studies randomizing patients to various IOH-CPB thresholds for CABG are warranted.

Appendix A. Supplementary material

Supplementary data are available in the online version of this article at http://dx.doi.org/10.1053/j.jvca.2016.07.040

References

1 Nichols M, Townsend N, Luengo-Fernandez R, et al: European Cardiovascular Disease Statistics 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis.

2 Schopka S, Diez C, Camboni D, et al. Impact of cardiopulmonary bypass on acute kidney injury following coronary artery bypass grafting: A matched pair analysis. J Cardiothorac Surg 2014;9(20):8090–9020.

3 Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol 2006;1:19–32.

4 Lenihan CR, Montez-Rath ME, Mora Mangano CT, et al. Trends in acute kidney injury, associated use of dialysis, and mortality after cardiac surgery, 1999 to 2008. Ann Thorac Surg 2013;95:20–8.

5 Lamy A, Devereaux PJ, Prabhakaran D, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med 2012;366:1489–97.

6 Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: Pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002;21:232–44.

7 Ranucci M, Aloisio T, Carboni G, et al. Acute kidney injury and hemodilution during cardiopulmonary bypass: A changing scenario. Ann Thorac Surg 2015;100:95–100.

8 Azau A, Markowicz P, Corbeau JJ, et al. Increasing mean arterial pressure during cardiac surgery does not reduce the rate of postoperative acute kidney injury. Perfusion 2014;29:496–504.

9 Gold JP, Charlson ME, Williams-Russo P, et al. Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. J Thorac Cardiovasc Surg 1995;110:1302–11.

10 Murphy GS, Hessel 2nd EA, Groom RC. Optimal perfusion during cardiopulmonary bypass: An evidence-based approach. Anesth Analg 2009;108:1394–417.

11 Kidney Disease. Improving global outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012;2:1–138.

12 Palomba H, de Castro I, Neto AL, et al. Acute kidney injury prediction following elective cardiac surgery: AKICS Score. Kidney Int 2007;72:624–31.

13 Berg KS, Stenseth R, Wahba A, et al. How can we best predict acute kidney injury following cardiac surgery?: A prospective observational study. Eur J Anaesthesiol 2013;30:704–12.

14 Li P, Stuart EA, Allison DB. Multiple imputation: A flexible tool for handling missing data. JAMA 2015;314:1966–7.

15 Rubin DB: Multiple imputation for non response in surveys. Wiley, New York, 1987.

16 Donders AR, van der Heijden GJ, Stijnen T, et al. Review: A gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087–91.

17 Knol MJ, Le Cessie S, Algra A, et al. Overestimation of risk ratios by odds ratios in trials and cohort studies: Alternatives to logistic regression. CMAJ 2012;184:895–9.

18 Karkouti K, Wijeysundera DN, Yau TM, et al. Acute kidney injury after cardiac surgery: Focus on modifiable risk factors. Circulation 2009;119:495–502.

19 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;119:507–15.

20 Sun LY, Wijeysundera DN, Tait GA, et al. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 2015;123:515–23.

21 Haase M, Bellomo R, Story D, et al. Effect of mean arterial pressure, haemoglobin and blood transfusion during cardiopulmonary bypass on post-operative acute kidney injury. Nephrol Dial Transplant 2012;27:153–60.

22 Sickeler R, Phillips-Bute B, Kertai MD, et al. The risk of acute kidney injury with co-occurrence of anemia and hypotension during cardiopulmonary bypass relative to anemia alone. Ann Thorac Surg 2014;97:865–71.

23 Kanji HD, Schulze CJ, Hervas-Malo M, et al. Difference between preoperative and cardiopulmonary bypass mean arterial pressure is independently associated with early cardiac surgery-associated acute kidney injury. J Cardiothorac Surg 2010;5:71.

24 O'Dwyer C, Woodson LC, Conroy BP, et al. Regional perfusion abnormalities with phenylephrine during normothermic bypass. Ann Thorac Surg 1997;63:728–35.

25 Boston US, Slater JM, Orszulak TA, et al. Hierarchy of regional oxygen delivery during cardiopulmonary bypass. Ann Thorac Surg 2001;71:260–4.