Association of Intraoperative Hypotension with Acute Kidney Injury after Elective Noncardiac Surgery

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ABSTRACT

Background: Intraoperative hypotension (IOH) may be associated with postoperative acute kidney injury (AKI), but the duration of hypotension for triggering harm is unclear. The authors investigated the association between varying periods of IOH with mean arterial pressure (MAP) less than 55, less than 60, and less than 65 mmHg with AKI.

Methods: The authors conducted a retrospective cohort study of 5,127 patients undergoing noncardiac surgery (2009 to 2012) with invasive MAP monitoring and length of stay of 1 or more days. Exclusion criteria were preoperative MAP less than 65 mmHg, dialysis dependence, urologic surgery, and surgical duration less than 30 min. The primary exposure was IOH. The primary outcome was AKI (50% or 0.3 mg/dl increase in creatinine) during the first 2 postoperative days. Multivariable logistic regression was used to model the exposure–outcome relationship.

Results: AKI occurred in 324 (6.3%) patients and was associated with MAP less than 60 mmHg for 11 to 20 min and MAP less than 55 mmHg for more than 10 min in a graded fashion. The adjusted odds ratio of AKI for MAP less than 55 mmHg was 2.34 (1.35 to 4.05) for 11- to 20-min exposure and 3.53 (1.51 to 8.25) for more than 20 min. For MAP less than 60 mmHg, the adjusted odds ratio for AKI was 1.84 (1.11 to 3.06) for 11- to 20-min exposure.

Conclusions: In this analysis, postoperative AKI is associated with sustained intraoperative periods of MAP less than 55 and less than 60 mmHg. This study provides an impetus for clinical trials to determine whether interventions that promptly treat IOH and are tailored to individual patient physiology could help reduce the risk of AKI. **(ANESTHESIOLOGY 2015; 123:515-23)**

ACUTE kidney injury (AKI) occurs in 7.5% of patients undergoing noncardiac surgery[1] and is associated with considerable short- and long-term mortality.[1–4] Surgical patients experiencing AKI postoperatively are eight times more likely to die within 30 days of surgery.[5] A recent meta-analysis demonstrated that hospitalized medical patients with an increase of more than 50% creatinine (Acute Kidney Injury Network [AKIN] stage I) were 6.9 times more likely to die (95% CI, 2.0 to 24.5).[3]

Perioperative hypotension is most prevalent during the intraoperative period[6] and may be an important determinant of postoperative AKI, as well as other postoperative complications.[1,2,4,7] Various definitions of intraoperative hypotension (IOH) have been evaluated in the literature,[8] with the most common definitions being a systolic blood pressure less than 80 mmHg, a mean arterial pressure (MAP) less than 55 to 60 mmHg, and a decrease in either systolic blood pressure or MAP of 25% from baseline.[2,8] However, the minimum magnitude and duration of hypotension needed to trigger harm is unclear. Walsh *et al.*,[7] in a large retrospective analysis, found a graded increase of AKI risk in patients with MAP less than 55 mmHg of more than 1 min and a modest risk of AKI with MAP of 55 to 59 mmHg lasting for more than 5 min. However, this study is inclusive of patients with baseline MAP less than the tested thresholds, excludes patients with baseline renal impairment, lacks a clear algorithm for filtering blood pressure (BP) artifacts that are

What We Already Know about This Topic

- Acute kidney injury (AKI) occurs in up to 7.5% of patients undergoing noncardiac surgery
- Perioperative hypotension may be an important determinant of postoperative AKI
- The minimum magnitude and duration of hypotension needed to trigger harm is unclear

What This Article Tells Us That Is New

- In a retrospective study of 5,127 patients undergoing noncardiac surgery, an increased risk of postoperative acute kidney injury (defined as more than 50% or 0.3 mg/dl increase in serum creatinine concentration) was found when intraoperative mean arterial pressure was less than 60 mmHg for more than 20 min and less than 55 mmHg for more than 10 min

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common occurrences in the intraoperative setting, and uses an expanded AKIN definition of AKI (*i.e.*, within the first 7 instead of 2 postoperative days). Increases in serum creatinine 7 days after surgery are likely subjected to confounding postoperative events that were independent of IOH. In addition, this definition of AKI likely carries a different prognostic significance compared with similar increases occurring within the first 2 days. As IOH is a potentially modifiable perioperative risk factor,[1,2,4,7,9] it is of paramount importance to determine the thresholds of IOH magnitude and duration that are associated with harm, using a more recent dataset over a narrower time interval, with the study objectives expanded to examine the association of IOH and AKI in patients with preoperative renal impairment. Moreover, reproducibility is an important scientific goal.

Therefore, we conducted a single-center retrospective cohort study to determine whether increasing durations of IOH are associated with postoperative AKI. Three thresholds of IOH magnitude were separately evaluated, namely MAP of 55, 60, and 65 mmHg. We hypothesized that increasing severity of IOH, both with respect to its magnitude (*i.e.*, lower BP) and duration (*i.e.*, longer periods of hypotension), was associated with higher risks of AKI.

Materials and Methods

Study Design and Cohort Selection

The University Health Network Research Ethics Board in Toronto, Ontario, Canada, approved this study and waived the need for informed consent. The University Health Network is a university-based tertiary care hospital that performs a full range of adult surgical procedures. We conducted a retrospective cohort study of all patients undergoing noncardiac surgery from November 2009 to December 2012, who were screened in the preoperative assessment clinic and had a length of stay of at least 1 day. To reduce the influence of varying accuracies across different intraoperative BP monitors, the cohort was restricted to those receiving invasive intraoperative BP monitoring. Exclusion criteria were baseline MAP less than 65 mmHg, preoperative dialysis dependence, and urologic surgery. Urologic procedures were excluded because associated changes in postoperative creatinine may be more directly related to the surgical intervention (*e.g.*, nephrectomy). Patients who did not have any postoperative creatinine measurements were assumed to not have AKI and were included in all analyses.

Data Sources

All perioperative data were prospectively collected and stored in three electronic databases, as a part of routine patient care. Preoperative information was extracted from the Clinical Anesthesia Information System (CAIS; Adjuvant Informatics, Freelton, Ontario, Canada). CAIS is a standardized web-based preoperative assessment tool used to evaluate elective surgical patients. Patient information is entered into CAIS by advanced practice nurses and anesthesiologists at prescheduled appointments. The collected data include demographics, vital signs, detailed medical histories, preoperative laboratory values, noninvasive tests, and medication histories, including whether patients were instructed to stop or continue medications before surgery.[10] At this preoperative assessment, all patients undergo noninvasive baseline BP measurement in both arms. All intraoperative invasive BP measurements are recorded automatically every minute into an electronic patient record using the EMR Lite software (Orion Health Ltd., Canada), with any artifacts removed using an automated algorithm. Time periods corresponding to absent (no MAP readings for 2 min or less) or aberrant MAP values (an isolated MAP value that differed more than 50% from preceding and subsequent values) were deleted. This approach conservatively biased the result toward the null. BP readings were analyzed from the onset of end-tidal carbon dioxide (*i.e.*, induction) until the last end-tidal carbon dioxide reading (*i.e.*, the conclusion of anesthesia and transfer of patient from the operating room to recovery unit). Postoperative information were extracted from the institutional electronic data warehouse (EDW) and included data relating to the surgical procedure, postoperative laboratory values, and postoperative outcomes. Aside from mortality, length of stay, and laboratory test values, postoperative outcomes in the EDW data are captured based on *International Classification of Diseases*, 10th revision diagnostic codes. We have recently shown an error rate less than 2% in a direct comparison of patient charts *versus* EDW data at our institution.[11]

Outcomes and Exposures

The primary outcome was AKI as diagnosed by the AKIN criteria[12] (50% relative or 0.3 mg/dl absolute increase in creatinine over the preoperative value during the first two postoperative days). Preoperative serum creatinine was measured at the time of the outpatient preoperative assessment.

Using intraoperative BP measurements in the EMR-Lite database, the primary exposure, namely IOH, was defined by MAP below one of three *a priori* designated thresholds (MAP of 55, 60, and 65 mmHg). These were selected based on thresholds shown to be associated with harm in recent studies.[2,7]

Statistical Analysis

Bivariable analyses were used to compare the characteristics of patients with and without IOH, for each of the prespecified hypotension thresholds. Continuous variables were analyzed using ANOVA and presented as mean (SD). Categorical variables were analyzed using chi-square test and presented as number (proportion).

We initially evaluated the unadjusted relationship between duration of time below each MAP threshold and the log odds of AKI using restricted cubic splines. For each MAP threshold, the log odds of AKI increased rapidly during the first 10 min of hypotension and slowly thereafter. Therefore, we categorized IOH duration as 0, 1 to 5, 6 to 10, 10 to 20, and more than 20 min.

The adjusted relationship between IOH and AKI was then modeled using multivariable logistic regression with adjustment for *a priori* selected risk factors for AKI. These risk factors included gender, comorbidities (*i.e.*, history of hypertension, coronary artery disease, heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, anemia, and malignancy), preoperative medications thought to be related to renal perfusion (*i.e.*, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers), preoperative renal function (categorized as estimated glomerular filtration rate [eGFR] greater than 60, 30 to 60, and less than 30 ml/min), and duration and type of surgery (general, thoracic, vascular, gynecological oncology, head and neck oncology, and plastics). Anemia was defined by the World Health Organization definition (less than 130 g/l for men and less than 120 g/l for women), based on the hemoglobin concentration measured at patients' outpatient preoperative anesthesia consultation. Preoperative renal function was characterized based on the eGFR calculated using the Cockcroft–Gault equation and serum creatinine available at patients' outpatient preoperative anesthesia consultation.

We tested for the presence of any interaction between IOH and preexisting hypertension. Measure of association was adjusted odds ratios (OR) and associated 95% CIs. This analytical approach was performed separately for each definition of IOH. Statistical significance was defined by a two-tailed $P < 0.05$.

Several sensitivity analyses were conducted to assess the robustness of our findings. First, to ensure the association of AKI with periods spent under higher tested MAP thresholds (*e.g.*, MAP < 65 mmHg) were not driven by periods spent below lower MAP thresholds (*e.g.*, MAP < 55 mmHg), we repeated the original multivariable analysis in subgroups of patients with MAP less than 55, 55 to 59, and 60 to 64 mmHg. We calculated the total number of minutes spent within each of these MAP "bands" and categorized these time periods using restricted cubic splines in a similar fashion as for the original analysis. Second, we repeated the multivariable analysis using AKIN stage 2 or higher AKI (two-fold increase in creatinine) during the first 2 postoperative days as the outcome. Third, we included intraoperative estimated blood loss, categorized by the surgical APGAR score definition,[13] as an additional covariate. Fourth, we excluded patients without any postoperative creatinine measurements. Fifth, we restricted our analyses to patients with normal preoperative renal function, as defined by eGFR more than 60 ml/min. All analyses were conducted using SAS version 9.1 (SAS Institute, USA).

Results

Of the 5,127 included patients, 324 (6.3%) developed AKI. Table 1 and Supplemental Digital Content 1, tables 1 and 2, http://links.lww.com/ALN/B171, summarize the baseline characteristics across time periods spent under all evaluated MAP thresholds. Table 2 summarizes the proportion of patients experiencing AKI based on the duration and magnitude of IOH. Table 3 compares the characteristics of patients with and without AKI.

There was a graded relationship between IOH (both with respect to its magnitude and duration more than 10 min) and odds of subsequent stage I postoperative AKI (table 4). For instance, stage I AKI was associated with MAP less than 55 and less than 60 mmHg for 11 to 20 min. A graded relationship exists between incremental durations of MAP less than 55 mmHg and the odds of stage I AKI. Compared with patients without IOH, the adjusted OR of AKI in patients with a MAP of less than 55 mmHg was 2.34 (95% CI, 1.35 to 4.05) for 11 to 20 min and 3.53 (95% CI, 1.51 to 8.25) for more than 20 min of exposure. Those with MAP of less than 60 mmHg for 11 to 20 min had an approximately twofold increased odds of stage I AKI. Male gender, history of hypertension, preoperative renal insufficiency (eGFR < 60 ml/min), anemia (World Health Organization definition; less than 130 g/l for men and less than 120 g/l for women), high-risk surgery (intraperitoneal, intrathoracic, and vascular), and longer surgery duration were also associated with stage I AKI. There was no interaction between preexisting hypertension and IOH.

When the odds of AKI were calculated in subgroups of patients with MAP bands of less than 55, 55 to 59, and 60 to 64 mmHg, patients with MAP less than 55 mmHg for 6 to 10 and more than 20 min, as well as patients with MAP of 55 to 59 and 60 to 64 mmHg for more than 20 min, were at an increased risk of stage I AKI (table 5). When the outcome was defined by moderate (AKIN stage II) AKI, MAP less than 60 and less than 65 mmHg were no longer risk factors for AKI, and only longer durations (greater than 20 min) of more severe IOH (MAP < 55 mmHg) were associated with harm (table 6). The association of IOH and stage II AKI is detailed in Supplemental Digital Content 1, table 3, http://links.lww.com/ALN/B171.

When estimated intraoperative blood loss was added to the primary model, MAP less than 55 mmHg for more than 11 min was associated with stage II AKI (table 6). The sensitivity model that is inclusive of intraoperative blood loss is detailed in Supplemental Digital Content 1, table 4, http://links.lww.com/ALN/B171. Intraoperative blood loss was a strong predictor of stage II AKI, and the addition of this variable had somewhat attenuated the association between IOH and AKI.

The associations between each of the three categories of IOH and stage I AKI were qualitatively and quantitatively preserved when analysis was restricted only to patients with postoperative creatinine measurements (n = 3,479; table 6). This sensitivity model is detailed in Supplemental Digital Content 1, table 5, http://links.lww.com/ALN/B171.

The exclusion of patients with abnormal preoperative renal function (eGFR ≤ 60 ml/min) had a small dampening effect on the association between IOH and stage I AKI (table 6). The sensitivity model that is restricted to patients

Table 1. Baseline and Intraoperative Characteristics by Durations of MAP < 55 mmHg

Variable	Duration of MAP < 55 mmHg (min)					
	0 (n = 1,597)	1–5 (n = 2,807)	6–10 (n = 500)	10–20 (n = 179)	>20 (n = 44)	*P* Value
Baseline						
Age (yr)	60.4 (14.0)	61.5 (14.2)	61.7 (14.7)	63.4 (14.9)	66.1 (15.7)	0.002
Female	894 (56.0%)	1,490 (53.1%)	215 (43.0%)	87 (48.6%)	22 (50.0%)	<0.001
Hypertension	759 (47.5%)	1,313 (46.8%)	245 (49.0%)	94 (52.1%)	26 (59.1%)	0.27
Coronary artery disease	189 (11.8%)	290 (10.3%)	60 (12.0%)	25 (14.0%)	9 (20.5%)	0.08
Heart failure	28 (1.8%)	23 (0.8%)	12 (2.4%)	4 (2.2%)	3 (6.8%)	<0.001
Peripheral vascular disease	141 (8.8%)	224 (8.0%)	32 (6.4%)	5 (2.8%)	3 (6.8%)	0.04
Cerebrovascular disease	51 (3.2%)	66 (2.4%)	4 (0.8%)	3 (1.7%)	2 (4.6%)	0.03
Chronic obstructive pulmonary disease	150 (9.4%)	231 (8.2%)	54 (10.8%)	12 (6.7%)	0 (0%)	0.05
Diabetes	229 (14.3%)	403 (14.4%)	74 (14.8%)	44 (24.6%)	14 (31.8%)	<0.001
Estimated glomerular filtration rate (ml/min)						
>60	1,366 (85.5%)	2,354 (83.7%)	403 (80.6%)	130 (72.6%)	33 (75.0%)	
30–60	212 (13.3%)	425 (15.1%)	86 (17.2%)	46 (25.7%)	8 (18.2%)	<0.001
<30	19 (1.2%)	28 (1.0%)	11 (2.2%)	3 (1.7%)	3 (6.8%)	
Anemia	189 (11.8%)	454 (16.2%)	108 (21.6%)	48 (26.8%)	13 (29.6%)	<0.001
Malignancy	756 (47.3%)	1,543 (55.0%)	300 (60.0%)	115 (64.2%)	28 (63.6%)	<0.001
Preoperative medications						
ACE inhibitor	259 (16.2%)	466 (16.6%)	85 (17.0%)	18 (10.1%)	12 (27.3%)	0.05
Angiotensin receptor blocker	147 (9.2%)	305 (10.9%)	70 (14.0%)	26 (14.5%)	8 (18.2%)	0.006
β Blocker	269 (16.8%)	415 (14.8%)	87 (17.4%)	35 (19.6%)	11 (25.0%)	0.06
Type of surgery						
General surgery	351 (22.0%)	757 (27.0%)	175 (35.0%)	51 (28.5%)	17 (38.6%)	
Vascular	201 (12.6%)	277 (9.9%)	40 (8.0%)	8 (4.5%)	4 (9.1%)	
Thoracic	440 (27.6%)	750 (26.7%)	114 (22.8%)	40 (22.4%)	3 (6.8%)	<0.001
Gynecological	367 (23.0%)	432 (15.4%)	39 (7.8%)	21 (11.7%)	4 (9.1%)	
Ear, nose, and throat	191 (12.0%)	455 (16.2%)	102 (20.4%)	51 (28.5%)	13 (29.6%)	
Plastic	47 (2.9%)	136 (4.9%)	30 (6.0%)	8 (4.5%)	3 (6.8%)	
Intraoperative						
Blood Loss (ml)						
≤100	44 (2.8%)	247 (8.8%)	68 (13.6%)	28 (15.6%)	9 (20.5%)	
101–600	61 (3.8%)	249 (8.9%)	51 (10.2%)	17 (9.5%)	2 (4.6%)	<0.001
601–1,000	470 (29.4%)	884 (31.5%)	166 (33.2%)	70 (39.1%)	16 (36.4%)	
>1,000	1,022 (64.0%)	1,427 (50.8%)	215 (43.0%)	64 (35.8%)	17 (38.6%)	
Duration of surgery (h)						
≤2	509 (31.9%)	498 (17.7%)	69 (13.8%)	19 (10.6%)	2 (4.6%)	
2–5	874 (54.7%)	1,350 (48.1%)	188 (37.6%)	69 (38.4%)	16 (36.4%)	<0.001
≥5	214 (13.4%)	959 (34.2%)	243 (48.6%)	91 (50.8%)	26 (59.1%)	

Anemia is defined by WHO (preoperative hemoglobin value of <130 g/l for men and <120 g/l for women). Estimated glomerular filtration rate is calculated using the Cockcroft–Gault formula.

ACE = angiotensin-converting enzyme; MAP = mean arterial pressure; WHO = World Health Organization.

with normal preoperative renal function is detailed in Supplemental Digital Content 1, table 6, http://links.lww.com/ALN/B171.

Discussion

In this single-center cohort study, postoperative AKIN stage I AKI was associated with intraoperative MAP of less than 55 mmHg for more than 10 min and MAP less than 60 mmHg for 11 to 20 min. These findings may help develop goal-directed intraoperative hemodynamic management strategies, because BP is one of very few modifiable intraoperative risk factors for adverse outcomes in the perioperative setting.

Our findings validate previously published single-center data from Walsh *et al.* Walsh *et al.*,[7] in a retrospective cohort of 18,989 noncardiac procedures, found graded relationship between the length of time spent with MAP less than 55 mmHg (OR, 1.51; 95% CI, 1.24 to 1.84) and MAP of 55 to 59 mmHg (OR, 1.65; 95% CI, 1.21 to 2.25) for more than 5 min and stage I AKI. Although this difference in the strength of association could be because of the exclusion of

Table 2. Proportion Experiencing AKI, Stratified by Hypotension Duration for MAP Thresholds of 55, 60, and 65 mmHg

	MAP < 55 mmHg		MAP < 60 mmHg		MAP < 65 mmHg	
IOH Duration (min)	N	AKI	N	AKI	N	AKI
1–5	2,807	189 (6.7%)	2,490	137 (5.5%)	1,474	64 (4.3%)
6–10	637	63 (9.9%)	1,030	64 (6.2%)	1,252	79 (6.3%)
11–20	63	7 (11.1%)	579	67 (11.6%)	1,182	80 (6.8%)
>20	23	4 (17.4%)	274	30 (11.0%)	903	92 (10.2%)

AKI = acute kidney injury; IOH = intraoperative hypotension; MAP = mean arterial pressure.

Table 3. Baseline and Intraoperative Characteristics of Patients with and without Postoperative AKI

Variable	AKI (n = 324)	No AKI (n = 4,803)	*P* Value
Baseline			
Age (yr)	58.9 (15.0)	59.5 (14.6)	0.49
Female	96 (29.6%)	2,621 (54.6%)	<0.001
Hypertension	229 (70.7%)	2,236 (46.6%)	<0.001
Preoperative medications			
ACE inhibitor	78 (24.1%)	767 (16.0%)	<0.001
Angiotensin receptor blocker	58 (17.9%)	506 (10.5%)	<0.001
β Blocker	89 (27.5%)	747 (15.6%)	<0.001
Coronary artery disease	58 (17.9%)	528 (11.0%)	<0.001
Heart failure	10 (3.1%)	66 (1.4%)	0.03
Peripheral vascular disease	45 (3.9%)	368 (7.7%)	<0.001
Cerebrovascular disease	6 (1.9%)	123 (2.6%)	0.47
Chronic obstructive pulmonary disease	34 (10.5%)	415 (8.6%)	0.37
Diabetes	85 (26.2%)	690 (14.4%)	<0.001
Estimated glomerular filtration rate (ml/min)			
>60	234 (72.3%)	4,023 (83.8%)	
30–60	70 (21.6%)	705 (14.7%)	<0.001
<30	20 (6.2%)	75 (1.6%)	
Anemia	92 (28.4%)	733 (15.3%)	<0.001
Malignancy	198 (61.1%)	2,553 (53.2%)	0.04
Type of surgery			
General surgery	130 (40.1%)	1,215 (25.3%)	
Vascular	52 (16.0%)	485 (10.1%)	
Thoracic	94 (29.0%)	1,249 (26.0%)	<0.001
Gynecological	27 (8.3%)	838 (17.4%)	
Ear, nose, and throat	20 (6.2%)	796 (16.6%)	
Plastic	1 (0.3%)	220 (4.6%)	
Intraoperative			
Blood Loss (ml)			
≤100	107 (33.0%)	2,646 (55.1%)	
101–600	92 (28.4%)	1,513 (31.5%)	<0.001
601–1,000	52 (16.0%)	324 (6.7%)	
>1,000	73 (22.5%)	320 (6.7%)	
Duration of surgery (h)			
≤2	28 (8.6%)	1,069 (22.3%)	
2–5	132 (40.7%)	2,365 (49.2%)	<0.001
≥5	164 (50.6%)	1,369 (28.5%)	

Anemia is defined by WHO (preoperative hemoglobin value of <130 g/l for men and <120 g/l for women). Estimated glomerular filtration rate is calculated using the Cockcroft–Gault formula.

ACE = angiotensin-converting enzyme; AKI = acute kidney injury; WHO = World Health Organization.

patients with preexisting renal insufficiency by Walsh *et al.*, the strength of association between IOH and stage I AKI was only slightly dampened in the present study when we restricted our analysis to patients with normal preoperative renal function. In addition, although intraoperative blood loss was shown in a sensitivity analysis to be a strong predictor of stage I AKI that also exerts a slight dampening effect on the IOH–AKI relationship, we did not include this variable in our primary analysis

Table 4. Association of Perioperative Characteristics with Postoperative Acute Kidney Injury

Variable	Adjusted OR (95% CI)		
	MAP < 55 mmHg	MAP < 60 mmHg	MAP < 65 mmHg
Baseline			
Female	0.42 (0.31–0.56)	0.42 (0.32–0.57)	0.42 (0.32–0.57)
Hypertension	1.97 (1.46–2.67)	1.96 (1.45–2.66)	2.01 (1.49–2.73)
Angiotensin-converting enzyme inhibitor	1.04 (0.75–1.45)	1.06 (0.76–1.46)	1.02 (0.74–1.42)
Angiotensin receptor blocker	1.21 (0.84–1.72)	1.21 (0.85–1.73)	1.19 (0.83–1.70)
β Blocker	1.33 (0.97–1.81)	1.33 (0.98–1.81)	1.32 (0.97–1.79)
Coronary artery disease	0.75 (0.52–1.07)	0.76 (0.53–1.09)	0.76 (0.53–1.09)
Heart Failure	1.20 (0.57–2.53)	1.17 (0.55–2.46)	1.15 (0.54–2.43)
Peripheral vascular disease	1.00 (0.54–1.82)	0.97 (0.53–1.77)	0.97 (0.53–1.77)
Cerebrovascular disease	0.42 (0.17–1.06)	0.42 (0.17–1.05)	0.42 (0.17–1.07)
Chronic obstructive pulmonary disease	0.92 (0.61–1.36)	0.91 (0.61–1.35)	0.90 (0.60–1.33)
Diabetes	1.23 (0.91–1.65)	1.24 (0.92–1.68)	1.24 (0.92–1.67)
Estimated glomerular filtration rate (ml/min)			
>60	Reference	Reference	Reference
30–60	1.46 (1.08–1.98)	1.47 (1.08–2.00)	1.47 (1.08–1.99)
<30	4.77 (2.67–8.50)	4.82 (2.71–8.57)	4.80 (2.69–8.55)
Anemia	1.44 (1.09–1.90)	1.42 (1.08–1.88)	1.43 (1.08–1.88)
Malignancy	1.17 (0.88–1.55)	1.17 (0.88–1.55)	1.17 (0.88–1.55)
Type of surgery			
General surgery	Reference	Reference	Reference
Vascular	1.05 (0.57–1.97)	1.07 (0.57–1.98)	1.07 (0.88–1.55)
Thoracic	1.05 (0.77–1.42)	1.04 (0.77–1.41)	1.03 (0.76–1.39)
Gynecological	0.76 (0.46–1.25)	0.78 (0.48–1.28)	0.78 (0.48–1.29)
Ear, nose, and throat	0.14 (0.09–0.23)	0.14 (0.09–0.23)	0.14 (0.09–0.23)
Plastic	0.07 (0.01–0.48)	0.07 (0.01–0.48)	0.06 (0.01–0.45)
Duration of surgery	2.41 (1.96–2.95)	2.42 (1.98–2.97)	2.37 (1.93–2.90)
Duration of intraoperative hypotension (min)			
None	Reference	Reference	Reference
1–5	1.35 (0.98–1.86)	1.10 (0.70–1.74)	1.28 (0.57–2.87)
6–10	1.45 (0.94–2.22)	1.08 (0.65–1.78)	1.56 (0.69–3.50)
11–20	2.34 (1.35–4.05)	1.84 (1.11–3.06)	1.57 (0.70–3.53)
>20	3.53 (1.51–8.25)	1.70 (0.93–3.10)	2.25 (0.99–5.07)

Acute kidney injury is defined by AKIN stage 1 criteria (0.3 mg/dl absolute or 50% relative increase in creatinine over the preoperative value) within 48 h of surgery. Anemia is defined by World Health Organization (preoperative hemoglobin value of <130 g/l for men and <120 g/l for women). Estimated glomerular filtration rate is calculated using the Cockcroft–Gault formula.

AKIN = Acute Kidney Injury Network; MAP = mean arterial pressure; OR = odds ratio.

Table 5. Comparison of Odds Ratios of Acute Kidney Injury across Mean Arterial Pressure "Bands" (*i.e.*, MAP <55, 55–59, and 60–64 mmHg)

Mean Arterial Pressure Band (mmHg)	Duration of Intraoperative Hypotension (min)				
	0	1–5	6–10	11–20	>20
<55	Reference	1.23 (0.87–1.74)	1.51 (1.00–2.30)	1.44 (0.94–2.19)	2.09 (1.40–3.11)
55–59	Reference	1.04 (0.67–1.62)	1.13 (0.69–1.84)	1.23 (0.77–1.97)	1.74 (1.13–2.69)
60–64	Reference	1.43 (0.68–3.00)	1.15 (0.53–2.50)	1.69 (0.83–3.43)	2.00 (1.01–3.95)

MAP = mean arterial pressure.

because of our inability to determine the temporal relationship between IOH and intraoperative blood loss. Kheterpal *et al.*,[14] in an observational study of 15,102 patients with normal preoperative renal function undergoing major noncardiac surgery, found that patients who suffered from AKI (defined as a calculated creatinine clearance of 50 ml/min or less) were more likely to have had more episodes of intraoperative MAP less than 40 mmHg. In an observational study of patients undergoing general surgery without any restriction on preoperative renal function, the same authors had found that patients with preoperative risk factors for AKI (defined as an increase in serum creatinine of at least 2 mg/dl or acute renal failure necessitating dialysis) were more likely to develop AKI if they had experienced periods of MAP less than 60 mmHg.[5]

Table 6. Comparison of Odds Ratios of Acute Kidney Injury across Primary and Sensitivity Analyses in Patients with Mean Arterial Pressure < 55 mmHg

	Duration of Intraoperative Hypotension (min)				
Analysis	0	1–5	6–10	11–20	>20
Primary analysis	Reference	1.35 (0.98–1.86)	1.45 (0.94–2.22)	2.34 (1.35–4.05)	3.53 (1.51–8.25)
AKIN stage II	Reference	0.79 (0.44–1.43)	1.29 (0.61–2.72)	0.79 (0.22–2.87)	4.86 (1.38–17.10)
Adjusted for intraoperative blood loss	Reference	1.24 (0.90–1.71)	1.28 (0.83–1.97)	2.04 (1.17–3.56)	3.11 (1.31–7.40)
Excluded patients without postoperative Cr measurement	Reference	1.33 (0.97–1.84)	1.41 (0.92–2.16)	2.10 (1.21–3.65)	3.53 (1.50–8.26)
Restricted to patients with preoperative eGFR > 60 ml/min	Reference	1.22 (0.85–1.77)	1.44 (0.88–2.35)	1.96 (0.99–3.88)	3.49 (1.25–9.74)

All models are age, gender, comorbidity, and surgery adjusted.

AKIN = Acute Kidney Injury Network; Cr = serum creatinine; eGFR = estimated glomerular filtration rate, as determined by the Cockcroft-Gault formula.

Our study demonstrates that the magnitude and duration of IOH are an important risk factor for both stage I and II AKI. This finding is biologically plausible. A historical animal study demonstrated a MAP of 50 to 60 mmHg to be the lower limit of autoregulation of renal blood flow.[15] It has been proposed that in adult human, renal blood flow remains constant between MAP of 75 and 170 mmHg, but becomes pressure dependent beyond this range.[16] Renovascular reactivity has recently been measured by near-infrared spectroscopy by Rhee *et al.*[17] This study demonstrated that in preterm piglets, renal blood flow decreased to 75, 50, and 25% of baseline, respectively, when MAP decreased to 60, 45, and 40 mmHg. In addition, renal perfusion is dependent on cardiac output. Patients become susceptible to AKI when MAP decreases below the lower threshold of the autoregulation curve, but AKI could occur in the presence of adequate MAP but poor cardiac output.[17] The complex and heterogeneous nature of individual patients' physiology in response to different anesthetic techniques further complicates this relationship. For instance, although IOH could be attributable to a low flow state secondary to anesthetics and preoperative medications such as β blockers, it could also be associated with a high cardiac output state such as in the case of neuraxial techniques. In addition, prompt treatment of IOH is more likely to improve patient outcome if the treatment is consistent with the underlying mechanism of hypotension. Furthermore, although we found a strong association between stage I AKI and short durations of MAP less than 55 mmHg, this study alone is unable to conclude whether AKI occurs as a direct consequence of IOH or as a consequence of the treatment of IOH, such as fluid and vasopressor administration. Numerous clinical studies have demonstrated deleterious renal effects of commonly administered resuscitation fluids, namely, synthetic colloids[18–23] and normal saline (*via* development of hyperchloremia).[24] In addition, evidence from animal models that renal blood flow remains unchanged with phenylephrine administration in animals with chronic hypertension,[25] and even increases with phenylephrine infusion in the context of sepsis.[26] Finally, the lower threshold of renal autoregulation is likely individual and not empiric. This is further supported by an increased incidence of cerebrovascular disease in patients with stage I AKI (table 1 and Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/B171). Thus, the ability to map individual threshold using surrogates such as cerebral autoregulation monitors may provide a more precise and individualized definition of IOH.[17,27] For these reasons, further research is needed to examine the mechanisms of IOH and real-time physiologic responses to common IOH treatment modalities and to develop proper treatment protocols that are tailored to individual patient physiology. Future research should also focus on the effect of *relative* hypotension on postoperative AKI, although this endeavor may be challenged by difficulty in determining true baseline BPs in the perioperative setting.

This study has several strengths. First, compared with other studies that included both invasive and noninvasive BP values, our inclusion of only invasively monitored patients reduces unmeasured confounding and gives us a less biased effect estimate. Second, we used prospectively collected patient data from elective preoperative assessments and EDWs, which, in addition to minimizing the various biases that are prevalent in observational studies, gave us an accurate record of baseline MAP, hemoglobin, and preoperative and postoperative creatinine values. Third, we had access to electronically recorded MAPs in a large number of patients on a per-minute basis and were able to remove most artifacts with designated software. This allowed us to define hypotensive episodes reliably. Fourth, the large sample size allowed for stable multivariable modeling. Specifically, there were 324 outcome events in our cohort. Thus, on the basis of 10 outcome events per predictor variable rule of thumb for achieving unbiased coefficient estimates,[28] we could include up to 32 predictor variables in our regression models. Fifth, the variety of included surgical procedures enhanced the generalizability of our findings.

Conversely, our study has a number of limitations that are representative of the limitations of observational studies. Because we had excluded patients with low baseline MAP, we are unable to deduce what degree of IOH could be tolerated in these patients. In addition, despite demonstrating a strong association between IOH and AKI,

this study alone is unable to conclude whether there is a subgroup of patients with IOH refractory to conventional therapy who would be more susceptible to AKI, and whether AKI occurs as a direct consequence of IOH or indirectly through associated factors (*e.g.*, low cardiac output, fluid and vasopressor administration). Because our study examined mostly patients undergoing elective procedures, we are unable to extrapolate our findings to those undergoing emergent procedures with confidence. Further, observational studies are by nature subject to residual confounding despite careful risk adjustment. Finally, invasively monitored patients are fundamentally a high-risk population by comorbidity and/or surgical complexity, and in whom hypotension is a highly anticipated event. This selection bias likely increased the magnitude of the association between IOH and AKI seen in the present study; however, this disadvantage was at least in part offset by a reduced degree of unmeasured confounding related to different MAP monitoring methods.

In conclusion, we found an increased risk of postoperative stage I AKI when intraoperative MAP was less than 60 mmHg for more than 20 min and less than 55 mmHg for more than 10 min. This study provides an impetus for clinical trials to determine whether interventions that promptly treat IOH and are tailored to individual patient physiology could help reduce the risk of these events.

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Competing Interests

The authors declare no competing interests.

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