

Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery

Toward an Empirical Definition of Hypotension

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ABSTRACT

Background: Intraoperative hypotension may contribute to postoperative acute kidney injury (AKI) and myocardial injury, but what blood pressures are unsafe is unclear. The authors evaluated the association between the intraoperative

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What We Already Know about This Topic

- Understanding intraoperative events that predict morbidity and mortality could improve perioperative care in surgical patients perhaps by preventing events or initiating treatments after adverse events

What This Article Tells Us That Is New

- This retrospective analysis examined mean arterial pressure to determine predictors of postoperative morbidity and mortality in noncardiac surgical patients in a database of more than 33,000 patients
- A mean arterial pressure less than 55 mmHg predicted adverse cardiac- and renal-related outcomes; however, the limitations of retrospective analyses must be considered

mean arterial pressure (MAP) and the risk of AKI and myocardial injury.

Methods: The authors obtained perioperative data for 33,330 noncardiac surgeries at the Cleveland Clinic, Ohio. The authors evaluated the association between intraoperative MAP from less than 55 to 75 mmHg and postoperative AKI and myocardial injury to determine the threshold of MAP where risk is increased. The authors then evaluated the association between the duration below this threshold and their outcomes adjusting for potential confounding variables.

Results: AKI and myocardial injury developed in 2,478 (7.4%) and 770 (2.3%) surgeries, respectively. The MAP threshold where the risk for both outcomes increased was

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 3A.

◆ This article is accompanied by an Editorial View. Please see: Brady K, Hogue CW Jr: Intraoperative hypotension and patient outcome: Does "one size fit all?" ANESTHESIOLOGY 2013; 119:495-7.

less than 55 mmHg. Compared with never developing a MAP less than 55 mmHg, those with a MAP less than 55 mmHg for 1–5, 6–10, 11–20, and more than 20 min had graded increases in their risk of the two outcomes (AKI: 1.18 [95% CI, 1.06–1.31], 1.19 [1.03–1.39], 1.32 [1.11–1.56], and 1.51 [1.24–1.84], respectively; myocardial injury 1.30 [1.06–1.5], 1.47 [1.13–1.93], 1.79 [1.33–2.39], and 1.82 [1.31–2.55], respectively).

Conclusions: Even short durations of an intraoperative MAP less than 55 mmHg are associated with AKI and myocardial injury. Randomized trials are required to determine whether outcomes improve with interventions that maintain an intraoperative MAP of at least 55 mmHg.

INTRAOPERATIVE hypotension has the potential to cause an ischemia–reperfusion injury which may manifest as dysfunction of any vital organ. Among the most sensitive organs to be affected in this way are the kidneys and the heart. However, blood pressures that constitute hypotension and provoke acute kidney and myocardial injury remain unclear.

Acute kidney injury (AKI), a sudden reduction in kidney function, occurs in approximately 7% of hospitalized patients and 7.5% of patients who undergo noncardiac surgery.^{1,2} Small changes in serum creatinine, the most commonly used marker of kidney function, are increasingly recognized as strong independent risk factors for short- and long-term mortality^{3,4} and more costly health care after surgery.^{2,5} Similarly, myocardial injury after noncardiac surgery manifests as an acute increase in the concentration of cardiac biomarkers and occurs in 11.6% of noncardiac surgeries.⁶ Myocardial injury after noncardiac surgery is also associated with a strong, independent risk of death after surgery, even with only small biomarker increases.⁶

Ischemia–reperfusion injury due to hypotension may substantially contribute to postoperative AKI and myocardial injury.⁷ As such, optimizing intraoperative hemodynamics may mitigate or prevent both complications. This theory is supported by a systematic review of interventions to prevent perioperative AKI that demonstrated maneuvers to prevent hypotension reduced the incidence of AKI,⁸ As well, as data from the Perioperative Ischemia Evaluation Trial demonstrated hypotension was the most responsible factor for postoperative death (of which, the majority were vascular).⁷

Although hypotension is recognized as an important factor in the development of postoperative complications, there is uncertainty in how to optimally define intraoperative hypotension. A systematic review on intraoperative hypotension identified 140 definitions used in 130 studies.⁹ Most of these definitions were not empirically derived, and each definition's association with clinical outcomes was explored in relatively few and/or small studies. We therefore studied patients who had noncardiac surgery to determine what durations of various levels of mean arterial pressure (MAP) are associated with AKI and myocardial injury to establish an empirical definition of prognostically important intraoperative hypotension.

Materials and Methods

Study Design

We undertook an observational study using data from the Cleveland Clinic Perioperative Health Documentation System, an electronic medical record-based registry of noncardiac surgery patients who had surgery between January 6, 2005 and September 21, 2010, at the Cleveland Clinic, Cleveland, Ohio. Use of this de-identified registry for research was approved by the Cleveland Clinic Institutional Review Board, Cleveland, Ohio.

Patients

Eligible patients had noncardiac surgery, stayed at least one night in hospital, and had a preoperative creatinine concentration measured and at least one postoperative creatinine. As chronic kidney disease may affect the interpretation and prognostic significance of absolute changes in serum creatinine and cardiac biomarkers, we excluded patients with chronic kidney disease, defined as an estimated preoperative glomerular filtration rate less than $60 \text{ ml}\cdot\text{min}^{-1}\cdot 1.73\text{m}^{-2}$. Patients having urological procedures such as the relief from urinary obstruction, nephrectomy, or renal transplantation were also excluded because of their association with changes in creatinine independent of renal injury.

Outcomes and Exposures

We defined AKI according to changes in serum creatinine between preoperative and postoperative values. The preoperative creatinine was considered to be the concentration measured closest to the time of surgery. The postoperative value used was the highest concentration measured within 7 days after surgery. Consistent with the Acute Kidney Injury Network threshold, patients were considered to have AKI if the highest postoperative concentration was either more than 1.5-fold or more than 0.3 mg/dl greater than the preoperative concentration.⁴ The small changes in creatinine used by this definition are independently associated with mortality in numerous studies.^{10–13}

We defined myocardial injury as a postoperative cardiac enzyme concentration within 7 days of surgery that was greater than or equal to the suggested necrosis limit for troponin T and greater than the upper limit of normal for creatinine kinase-MB. For a fourth-generation troponin T assay (Roche Diagnostics, Mannheim, Germany), this was 0.04 µg/l or more and for creatine kinase-MB 8.8 ng/ml or more. These definitions are consistent with the universal definition of myocardial infarction and data from a large international study on perioperative myocardial infarction.^{6,14} Rather than exclude patients who were otherwise eligible but did not have any cardiac enzymes measured, we assumed these patients did not have a myocardial injury and included them in all analyses.

As a secondary outcome, we also examined the association between intraoperative blood pressure and the outcome of a postoperative cardiac complication as defined by the Agency for Healthcare Research and Quality using administrative

codes for complications of surgical procedures. §§ This definition includes intraoperative and postoperative acute myocardial infarctions, heart failure, and cardiac arrest.

Intraoperative Blood Pressure

The intraoperative MAP was recorded electronically for all cases directly into an electronic medical record. When an arterial catheter was used (44.5% of cases), MAP was recorded every 1–2 min. When noninvasive blood pressure monitoring was used, MAP was recorded from every 2–5 min. During minutes when no blood pressure was recorded or when a reading was marked as artifact by the attending anesthesiologist, the last nonartifact blood pressure was carried forward.

For each case, we calculated the total number of minutes spent with a MAP less than 55, less than 60, less than 65, less than 70, and less than 75 mmHg. For each case, we also calculated the number of minutes during which the MAP was less than 55, 55–59, 60–64, 65–69, 70–74, and 75 mmHg or more.

Other Exposures

Patient's age and sex were determined from the registry. The Charlson Comorbidity Index and Risk Stratification Index for 30-day mortality and validated risk scores using administrative data codes were calculated for all patients.^{15,16} Preoperative kidney function was characterized according to the patient's estimated glomerular filtration rate using the four-variable Modification of Diet in Renal Disease equation.¹⁷ Preoperative hemoglobin was categorized according to the hemoglobin concentration taken closest to the time before surgery. Intraoperative estimated blood loss and transfusion of erythrocytes (autologous and allogeneic) were recorded in the clinical database. We previously demonstrated that decrements in hemoglobin concentration in the first 24 h after surgery are strongly associated with AKI, so this parameter was also included in the model. Surgeries were classified according to the Agency for Healthcare Research and Quality descriptors and whether they were emergency or elective procedures.

Statistics

Patient characteristics were calculated as mean (SD), median (25th to 75th percentile), or frequency (%) as appropriate. Comparisons of patient characteristics between groups were made using ANOVA for continuous data and the chi-square test for frequency data.

We visually assessed the relationship between the total amount of time spent under each MAP threshold (<55, <60, <65, <70, and <75 mmHg) and each outcome using restricted cubic splines in a logistic regression model. For each threshold, risk appeared to initially substantially increase rapidly for each minute under the threshold for

approximately 10 min, followed by a less rapid risk increase thereafter. We therefore categorized patients as having spent 0, 1–5, 6–10, 11–20, or more than 20 min in each strata. We were concerned that the association between time spent under each threshold may be due to time spent well beneath that threshold rather than just under the threshold value (*i.e.*, an association between time under a MAP of 65 mmHg may be due to time spent with a MAP less than 55 mmHg rather than the time spent with a MAP between 55 and 65 mmHg). We therefore conducted several further analyses to more accurately determine the blood pressure threshold that was most clinically relevant.

Using logistic regression model, we next explored whether the risk for each category was in fact driven by the lowest MAPs by: (1) calculating the risk of AKI and separately myocardial injury associated with the amount of time each patient spent with a MAP in each strata (*i.e.*, <55, 55–59, 60–64, 65–69, and 70–74 mmHg) while excluding patients with any time spent in lower blood pressure strata (*i.e.*, only patients with a lowest blood pressure in a given strata or higher strata remained in the analysis); (2) calculating the risk of AKI and separately myocardial injury for the time spent in each blood pressure strata while adjusting for time spent in the other strata; and (3) calculating separately the risk of AKI and myocardial injury by the lowest MAP during surgery irrespective of the amount of time at that blood pressure.

On the basis of these models, we then constructed final logistic models using the amount of time spent with a MAP below the highest threshold MAP that was predictive of one of the outcomes categorized as 0, 1–5, 6–10, 11–20, or more than 20 min below that threshold. The final model was adjusted for age, sex, the Charlson Comorbidity Index, the volume of erythrocytes transfused intraoperatively, estimated blood loss, preoperative hemoglobin, decrement in hemoglobin within 24 h of surgery, and the type of surgery performed. We *a priori* tested for interactions between duration of a MAP below threshold and emergency surgery status and decrement in hemoglobin concentration and dropped these interaction terms when they were found to be non-significant. We accommodated the correlation of multiple surgeries at different times for an individual by calculating estimated standard errors adjusted for intragroup correlations using clustered sandwich estimators.^{18,19} We reported adjusted odds ratios and associated 95% CIs and *P* values. We tested the trend of increasing risk with increasing time with a MAP less than 55 mmHg using the Cochran–Armitage test for trend. We set the criterion for statistical significance at *P* value less than 0.05 for all tests.

We performed sensitivity analyses to assess the robustness of our findings. Sensitivity models were constructed as logistic regression identical to the final model above, except: (1) with the primary outcome AKI redefined on the basis of postoperative creatinine concentrations only up to 3 days postoperatively; (2) using severe AKI (three-fold increase in

§§ Available at: <http://www.hcup-us.ahrq.gov/toolsoftware/ccs/>. Accessed October 28, 2011.

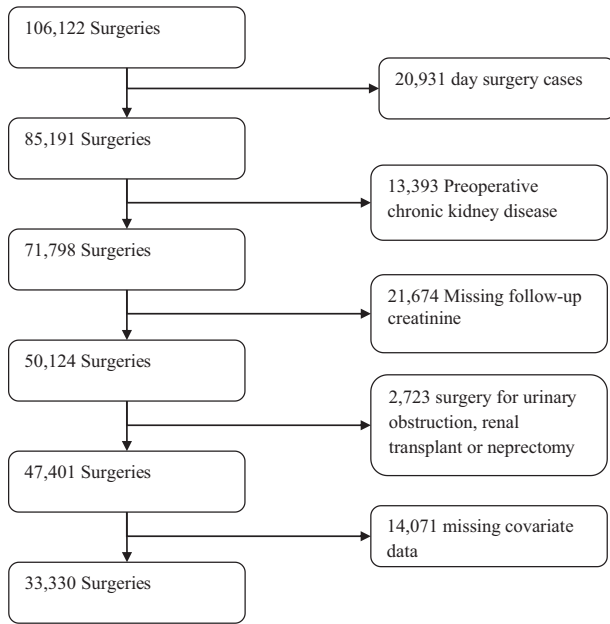


Fig. 1. Patient selection.

creatinine) as the outcome; (3) using the Risk Stratification Index rather than the Charlson Comorbidity Index; (4) restricting the analysis of myocardial injury to only those patients with a troponin T measured; (5) adjusting for systolic blood pressure recorded in the Preoperative Clinic for patients in whom this was recorded; (6) adjusting for the duration of the surgery; (7) using multiple imputation of missing covariate data; and (8) using only one surgery per patient (the most recent surgery). We completed all analyses using Stata version 11 MP (College Station, TX).

Results

Figure 1 reports the patient flow chart. In total, we included 33,330 surgeries performed in 27,381 patients in the analysis. Compared with patients in excluded surgeries, the included patients were younger, had lower American Society

of Anesthesiology Status Scores, and less comorbidity but had longer operations and postoperative lengths of stay (data not shown). AKI occurred after 2,477 surgeries (7.4%) of which 2,043 (82.4%) occurred within 3 days of surgery. Myocardial injury was documented in 770 surgeries (2.3%), and 926 (2.8%) had a cardiac complication after surgery. Five hundred six patients (1.5%) died within 30 days of surgery.

Defining Hypotension

Point estimates for the risk of AKI and myocardial injury minimally increased with the amount of time spent under each MAP threshold, and was pronounced for any time spent with a MAP less than 60 mmHg (fig. 2). The risks appeared nonlinear in each model ($P < 0.001$ in every model) with risk increasing markedly during the first 10 min, but at a slower rate thereafter. In multivariable spline models in which we controlled for the amount of time spent in each MAP category, the risk of AKI appeared greater for time spent with a MAP less than 60 mmHg and the risk of myocardial injury appeared greater only for a MAP less than 55 mmHg (fig. 3).

We then performed analyses in which we excluded patients who had any time in the lowest MAP category (*i.e.*, MAP <55 mmHg for any duration). These analyses were performed to ensure that correlations between time below a MAP of 55 mmHg and time spent in other blood pressure strata did not cause us to miss significant associations between a MAP more than 55 mmHg and our outcomes. In the 18,989 eligible surgeries, there was a modest but statistically significant risk of AKI for a MAP of 55–59 mmHg lasting longer than 5 min (adjusted odds ratios, 1.65; 95% CI, 1.21–2.25; $P = 0.002$). However, there was no additional risk in the time categories more than 10 min for a MAP of 55–59 mmHg and there was no risk of AKI in higher MAP categories (*i.e.*, MAP ≥ 60 mmHg). There was no risk of myocardial injury associated with any MAP range or duration once periods of MAP less than 55 mmHg were excluded.

Finally, we performed univariable spline analyses in which the lowest MAP for the surgery was the predictor of

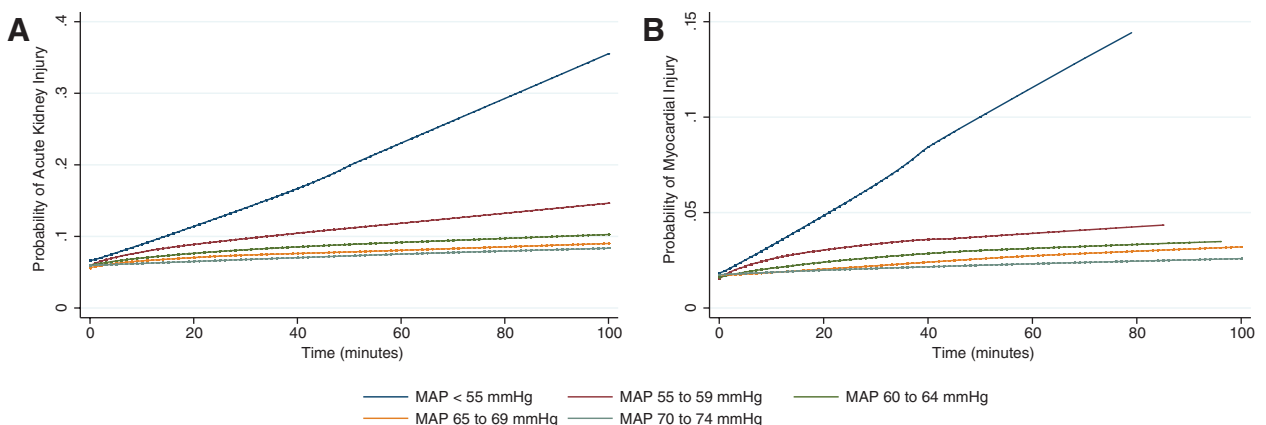


Fig. 2. Predicted risk of (A) acute kidney injury and (B) myocardial injury for each minute the mean arterial pressure (MAP) is <55 mmHg, between 55 and 59 mmHg, between 60 and 64 mmHg, between 65 and 69 mmHg, and between 70 and 74 mmHg during noncardiac surgery. The risk for time in each blood pressure strata is adjusted for time in all other blood pressure strata.

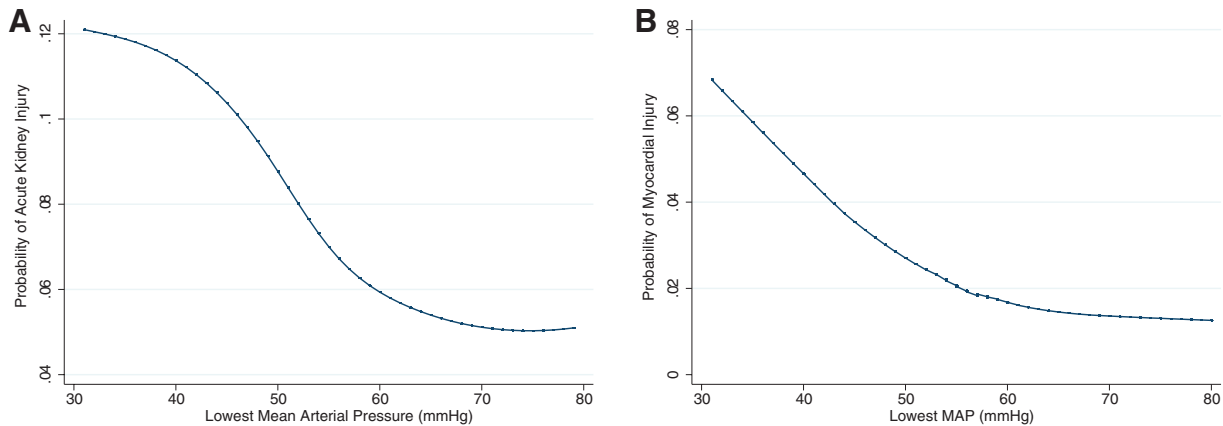


Fig. 3. Predicted probability of (A) acute kidney injury and (B) myocardial injury by lowest mean arterial pressure (MAP) experienced during surgery.

AKI and myocardial injury. The risk of both AKI and myocardial injury appeared to increase substantially at MAPs less than 55–60 mmHg (fig. 4).

On the basis of these analyses, for the final models we categorized patients by the amount of time they spent with a MAP less than 55 mmHg as 0, 1–5, 6–10, 11–20, and more than 20 min.

Patients with different amounts of time with a MAP less than 55 mmHg differed significantly with respect to most characteristics (table 1). However, only emergency procedures, preoperative hemoglobin, and intraoperative estimated blood loss appeared to have a clear progression as time with a MAP less than 55 mmHg increased (*i.e.*, more emergency procedures, lower hemoglobin, and larger estimated blood loss).

Risk of AKI, Myocardial Injury, Cardiac Complications, and 30-day Mortality with Hypotension

In our fully adjusted model, we observed an independent, graded relationship between the length of time spent with a MAP less than 55 mmHg and AKI and cardiac complications (table 2 and fig. 4). A similar magnitude of association was

seen for myocardial injury although the relationship was less graded as time with a MAP less than 55 mmHg increased. Compared with patients who spent no time with a MAP less than 55 mmHg, those with the longest periods of a MAP less than 55 mmHg had approximately a 1.5-fold increased risk of AKI or myocardial injury and an almost two-fold increased risk of a cardiac complication. The test for trend across durations of MAP less than 55 mmHg was *P* value less than 0.001 for all three outcomes. These relationships were qualitatively preserved across sensitivity analyses (tables 3 and 4). Of note, although the absolute risk of AKI and myocardial injury was increased in patients in the highest quartile of preoperative clinic blood pressures, the relative effect of each period of time spent with a MAP less than 55 mmHg was preserved across all baseline blood pressures, and there was no evidence of interaction between preoperative blood pressure and time with a MAP less than 55 mmHg (*P* > 0.1 for all interaction groups).

As time increased with a MAP less than 55 mmHg, there was a trend to a higher risk of death by 30 days after surgery (test for trend, *P* < 0.001). However, 30-day mortality was only significantly associated with more than 20 min of MAP less than 55 mmHg (table 2).

Discussion

In this large cohort with detailed intraoperative blood pressures, we found that MAP less than 55 mmHg was associated with the development of AKI, myocardial injury, and cardiac complications. Furthermore, we found that risk escalates rapidly and there does not appear to be any safe duration of a MAP less than 55 mmHg. This finding is important because AKI and myocardial injury are common, strongly associated with morbidity and mortality, and costly. Unlike baseline patient characteristics which are rarely modifiable, intraoperative MAP can usually be controlled and may thus be an important therapeutic target. Understanding what arterial pressures are associated with ischemic damage will help guide interventional studies.

Our study differs from many others in that we account for each minute spent with a MAP less than 55 mmHg which

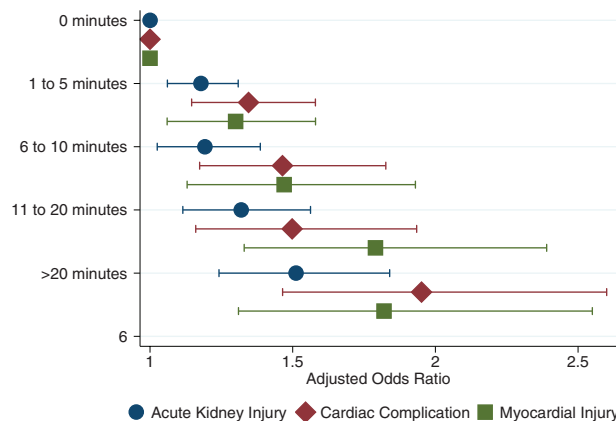


Fig. 4. Adjusted odds ratios for acute kidney injury, cardiac complications, and myocardial injury by time spent with a mean arterial pressure <55 mmHg.

Table 1. Patient Characteristics by Operative Time Spent with a MAP <55 mmHg

	MAP <55 mmHg					P Value
	Never n = 18,989	1–5 min n = 8,266	6–10 min n = 2,856	11–20 min n = 1,987	>20 min n = 1,232	
Age, yr*	54.8 (15.3)	57.3 (15.5)	57.9 (15.6)	56.1 (16.6)	55.7 (16.7)	<0.001
Female, n (%)	9,519 (50.0)	4,102 (49.6)	1,516 (53.1)	1,064 (53.5)	635 (51.5)	<0.001
Emergency procedure, n (%)	1,063 (5.6)	579 (7.0)	193 (6.8)	188 (9.5)	144 (11.7)	<0.001
ASA score, n (%)						
I	418 (2.2)	121 (1.4)	42 (1.5)	26 (1.3)	16 (1.3)	<0.001
II	8,262 (43.6)	2,965 (35.9)	1,022 (35.8)	652 (32.8)	347 (28.2)	
III	9,120 (48.1)	4,387 (53.1)	1,521 (53.3)	1,087 (54.7)	654 (53.1)	
IV	1,143 (6.0)	767 (9.3)	264 (9.2)	218 (11.0)	211 (17.1)	
V	28 (0.1)	24 (0.3)	7 (0.2)	4 (0.2)	4 (0.3)	
Charlson Index†	0 (0 to 2)	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)	<0.001
Diabetes mellitus, n (%)	2,424 (12.8)	1,056 (12.8)	384 (13.4)	246 (12.4)	156 (12.7)	0.71
Myocardial infarction, n (%)	699 (3.7)	387 (4.7)	143 (5.0)	88 (4.4)	43 (3.5)	<0.001
Congestive heart failure, n (%)	581 (3.1)	302 (3.7)	90 (3.2)	85 (4.3)	43 (3.5)	<0.001
Peripheral vascular disease, n (%)	576 (3.0)	474 (5.7)	150 (5.3)	97 (4.9)	57 (4.6)	<0.001
Stroke, n (%)	796 (4.2)	495 (6.0)	150 (5.2)	88 (4.4)	84 (6.8)	<0.001
Estimated GFR, ml·min ⁻¹ ·73m ⁻² *	92.3 (26.3)	91.7 (26.7)	93.2 (29.6)	94.9 (32.2)	96.6 (33.8)	<0.001
Hemoglobin, g/dl*	13.1 (2.0)	13.0 (2.0)	12.8 (2.1)	12.6 (2.1)	12.3 (2.1)	<0.001
Intraoperative erythrocyte transfusions, ml†	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 320)	0 (0 to 690)	<0.001
Estimated blood loss, ml†	200 (80 to 350)	250 (100 to 550)	250 (100 to 600)	300 (100 to 700)	400 (163 to 1,000)	<0.001

P values for continuous data computed by ANOVA. P values for frequency data computed by chi-square test.

* Mean (SD). † Median (first to third quarter).

ASA = American Society of Anesthesiologists; GFR = glomerular filtration rate; MAP = mean arterial pressure.

appears to be an especially sensitive method of determining the effect of MAP on the kidneys and heart. Our findings that a MAP less than 55 mmHg is strongly associated with renal and cardiac risks are nonetheless broadly consistent with previous work. Classic physiology experiments, for example, suggested that renal blood flow is maintained (autoregulated) down to a MAP of 50–60 mmHg.^{20,21} However, this inference is extrapolated from experiments in healthy animals.

In critically ill patients, one study in 217 patients found a MAP of up to 82 mmHg may be required to prevent AKI.²² Similarly, a study in 31 critically ill patients demonstrated periods with a systolic blood pressure less than

90 mmHg for at least 30 min were associated with higher levels of cardiac enzymes. However, critically ill patients may have more confounding influences than the generally healthier population we studied. One study performed in patients undergoing noncardiac surgery found that in those who were at high risk for AKI, periods of a MAP less than 60 mmHg were more common in those who developed AKI than those who did not.²³ Furthermore, using classification and regression tree analysis, Bijker *et al.*²⁴ found a MAP less than 50 mmHg had the largest independent association with death in their study in 1,705 patients undergoing noncardiac surgery. However, there were only 88 deaths in the

Table 2. Adjusted Odds Ratios for Acute Kidney Injury, Myocardial Injury, and Cardiac Complications for Intraoperative Time Spent with a MAP <55 mmHg

Time MAP <55 mmHg (min)	Adjusted Odds Ratio (95% CI)			
	Acute Kidney Injury	Myocardial Injury	Cardiac Complication	30-day Mortality
0	Referent			
1–5	1.18 (1.06–1.31)	1.30 (1.06–1.58)	1.35 (1.15–1.58)	1.16 (0.91–1.46)
6–10	1.19 (1.03–1.39)	1.47 (1.13–1.93)	1.46 (1.17–1.83)	1.16 (0.84–1.60)
11–20	1.32 (1.11–1.56)	1.79 (1.33–2.39)	1.50 (1.16–1.94)	1.26 (0.89–1.80)
>20	1.51 (1.24–1.84)	1.82 (1.31–2.55)	1.95 (1.46–2.60)	1.79 (1.21–2.65)

Estimates adjusted for patient age, sex, Charlson comorbidity index, emergency procedure status, type of surgery, preoperative hemoglobin, decrement in hemoglobin concentration, estimated blood loss, and volume of erythrocyte transfusions.

MAP = mean arterial pressure.

Table 3. Comparison of Results for Primary Analysis of Acute Kidney Injury Outcome Compared with Sensitivity Analyses

		Time Mean Arterial Pressure <55 mmHg (min)				
		0	1–5	6–10	11–20	>20
Primary	Referent	1.18 (1.06–1.31)	1.19 (1.03–1.39)	1.32 (1.11–1.56)	1.51 (1.24–1.84)	
AKI within 3 d	Referent	1.15 (1.02–1.29)	1.15 (1.00–1.35)	1.30 (1.09–1.56)	1.45 (1.17–1.80)	
Severe AKI	Referent	1.05 (0.77–1.50)	1.70 (1.16–2.63)	1.20 (0.70–2.11)	1.31 (0.72–2.37)	
Adjusted for RSI	Referent	1.12 (1.01–1.25)	1.13 (1.00–1.32)	1.23 (1.04–1.46)	1.36 (1.12–1.66)	
Adjusted for preoperative systolic blood pressure	Referent	1.19 (1.07–1.33)	1.17 (1.00–1.38)	1.30 (1.10–1.56)	1.55 (1.26–1.91)	
Adjusted for case duration	Referent	1.11 (1.00–1.24)	1.12 (0.97–1.30)	1.22 (1.03–1.45)	1.33 (1.09–1.62)	
Multiple imputation of missing covariates	Referent	1.24 (1.12–1.37)	1.25 (1.09–1.45)	1.38 (1.18–1.63)	1.58 (1.31–1.91)	
Most recent surgery only	Referent	1.10 (0.99–1.26)	1.07 (0.90–1.29)	1.36 (1.10–1.68)	1.33 (1.03–1.71)	

All models are adjusted for patient age, sex, preoperative hemoglobin, Charlson Comorbidity score (except RSI model), preoperative hemoglobin, estimated blood loss, transfusions, emergency surgery, and type of surgery.

AKI = acute kidney injury; RSI = risk stratification index.

study and it was therefore likely underpowered to show an association between a low intraoperative MAP and death at 1 yr. Another study found that periods of clinically significant hypotension corresponding to a systolic blood pressure less than 90 mmHg requiring treatment were a strong determinant of postoperative death; however, this study did not assess the association between hypotension and myocardial injury or hypotension and AKI.⁷ Our study extends previous work and informs the degree and duration of low MAP that is clinically important and suggests that hypotension is independent of other risk factors in a diverse cohort of non-cardiac surgical patients. Furthermore, our cohort is among the largest and therefore capable of detecting modest effects of low blood pressure on clinical events that occur close to the time of surgery.

Most studies examining risk factors for postoperative complications such as myocardial events and AKI concentrate on

preoperative morbidity. Although preoperative patient characteristics allow us to appropriately stratify the risk of myocardial events and AKI, they provide few risk factors that are potentially modifiable. Intraoperative and early postoperative risk factors may improve risk stratification and provide important therapeutic targets. By understanding at what level of MAP ischemia–reperfusion injury becomes likely, it is possible to focus interventions on patients most likely to benefit. This is a promising target for intervention as shown in small trials of hemodynamic optimization.⁸

Our study has several notable strengths. We used electronically recorded blood pressures which were available on a minute-by-minute basis in 14,828 patients and every 2–5 min in the remaining patients. These detailed records allowed us to characterize intraoperative hemodynamics in considerable detail. Our large sample size provided sufficient statistical power to fit a stable model

Table 4. Comparison of Results for Primary Analysis of Myocardial Injury Outcome Compared with Sensitivity Analyses

		Time Mean Arterial Pressure <55 mmHg (min)				
		0	1–5	6–10	11–20	>20
Primary	Referent	1.30 (1.06–1.58)	1.47 (1.13–1.93)	1.79 (1.34–2.39)	1.82 (1.31–2.55)	
Restricted to patients with troponin T measured (n = 4,533)	Referent	0.99 (0.80–1.20)	1.12 (0.84–1.50)	1.32 (1.00–1.79)	1.35 (0.99–1.90)	
Adjusted for RSI	Referent	1.21 (0.99–1.48)	1.35 (1.03–1.78)	1.60 (1.22–2.10)	1.67 (1.23–2.25)	
Adjusted for preoperative systolic blood pressure	Referent	1.15 (0.95–1.43)	1.26 (0.96–1.70)	1.54 (1.15–2.08)	1.56 (1.11–2.17)	
Adjusted for case duration	Referent	1.27 (1.05–1.53)	1.44 (1.12–1.86)	1.72 (1.30–2.26)	1.89 (1.39–2.58)	
Multiple imputation of missing covariates	Referent	1.31 (1.10–1.57)	1.48 (1.16–1.89)	1.85 (1.42–2.40)	2.03 (1.51–2.72)	
Most recent surgery only	Referent	1.21 (0.97–1.52)	1.05 (0.75–1.47)	1.51 (1.08–2.13)	1.58 (1.07–2.32)	

All models are adjusted for patient age, sex, preoperative hemoglobin, Charlson Comorbidity score (except RSI model), preoperative hemoglobin, estimated blood loss, transfusions, emergency surgery, and type of surgery.

RSI = risk stratification index.

despite numerous covariates, and thus detect even moderate associations between intraoperative blood pressures and AKI and myocardial injury. Our sample included a broad spectrum of patients in terms of surgical types and comorbidities, thereby making our findings generalizable. And finally, our results were consistent across numerous sensitivity analyses testing important assumptions related to our primary analysis.

An important limitation of our analysis is that observed associations could result from residual confounding. For example, we were not able to incorporate perioperative medication effects such as angiotensin-converting enzyme inhibitors or angiotensin-receptor antagonists which may be important in the pathogenesis of both intraoperative hypotension and AKI.^{25,26} Although the observed association may not be causal, and the treatments used for low MAP may account for some of the observed associations, there is a strong biologic plausibility for the effect we saw and it was consistent across all analyses. The association between time spent with a MAP less than 55 mmHg and both AKI and myocardial injury were of moderate size. Although it is probable that residual confounding accounts for at least part of the observed associations, the fact that our findings were consistent across outcomes and sensitivity analyses suggests an underlying biologic effect. Our study was only from a single center, which may reduce the generalizability, although we would expect that a physiologic parameter like MAP should have consistent effects across centers. We also need to be cautious applying our findings to groups of patients and to outcomes not included in our study. As we excluded patients with abnormal renal function preoperatively and patients who did not have postoperative serum creatinine measurements (and who were therefore likely healthier and/or underwent less complicated procedures), our empiric definition of hypotension needs to be studied in these patients. Similarly, we lack data on stroke outcomes. Importantly, our results provide information on what the average tolerated MAP may be in patients having noncardiac surgery. Individuals tolerated limits will vary. But currently, there are not specific data indicating how thresholds may vary or that would allow clinicians to determine the threshold in a specific patient. Finally, we have not yet validated our finding in an independent cohort.

In summary, we found that time spent with a MAP less than 55 mmHg during noncardiac surgery is independently associated with an increased risk of AKI and myocardial injury. Notably, any amount of time at a MAP less than 55 mmHg was associated with adverse outcomes. Further research is required to determine whether interventions to prevent and rapidly treat intraoperative hypotension ameliorate the risk of AKI and myocardial injury in patients having noncardiac surgery.

References

1. Abelho FJ, Botelho M, Fernandes V, Barros H: Determinants of postoperative acute kidney injury. *Crit Care* 2009; 13:R79
2. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW: Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; 16:3365–70
3. Bellomo R, Kellum JA, Ronco C: Defining and classifying acute renal failure: From advocacy to consensus and validation of the RIFLE criteria. *Intensive Care Med* 2007; 33:409–13
4. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network: Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11:R31
5. Davenport DL, Henderson WG, Khuri SF, Mentzer RM Jr: Preoperative risk factors and surgical complexity are more predictive of costs than postoperative complications: A case study using the National Surgical Quality Improvement Program (NSQIP) database. *Ann Surg* 2005; 242:463–8; discussion 468–71
6. Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccari BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati BG, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le MY, Leuw M, Yusuf S: Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; 307:2295–304
7. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. *Lancet* 2008; 371:1839–47
8. Brienza N, Giglio MT, Marucci M, Fiore T: Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med* 2009; 37:2079–90
9. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ: Incidence of intraoperative hypotension as a function of the chosen definition: Literature definitions applied to a retrospective cohort using automated data collection. *ANESTHESIOLOGY* 2007; 107:213–20
10. Ricci Z, Cruz D, Ronco C: The RIFLE criteria and mortality in acute kidney injury: A systematic review. *Kidney Int* 2008; 73:538–46
11. Coca SG, Peixoto AJ, Garg AX, Krumholz HM, Parikh CR: The prognostic importance of a small acute decrement in kidney function in hospitalized patients: A systematic review and meta-analysis. *Am J Kidney Dis* 2007; 50:712–20
12. Chung KK, Stewart IJ, Gisler C, Simmons JW, Aden JK, Tilley MA, Cotant CL, White CE, Wolf SE, Renz EM: The Acute Kidney Injury Network (AKIN) criteria applied in burns. *J Burn Care Res* 2012; 33:483–90
13. Kim WY, Huh JW, Lim CM, Koh Y, Hong SB: A comparison of acute kidney injury classifications in patients with severe sepsis and septic shock. *Am J Med Sci* 2012; 344:350–6
14. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernández-Avilés F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I,

- Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: Universal definition of myocardial infarction. *Circulation* 2007; 116:2634–53
15. Sessler DI, Sigl JC, Manberg PJ, Kelley SD, Schubert A, Chamoun NG: Broadly applicable risk stratification system for predicting duration of hospitalization and mortality. *ANESTHESIOLOGY* 2010; 113:1026–37
 16. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V: Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011; 173:676–82
 17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130:461–70
 18. Huber PI: The behavior of maximum likelihood estimates under nonstandard conditions. *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability*. 1967; 1:221–33
 19. Rogers WH: Regression standard errors in clustered samples. *Stata Technical Bulletin* 1993; 13:19–3
 20. Bayliss WM: On the local reactions of the arterial wall to changes of internal pressure. *J Physiol* 1902; 28:220–31
 21. Harper AM: Autoregulation of cerebral blood flow: Influence of the arterial blood pressure on the blood flow through the cerebral cortex. *J Neurol Neurosurg Psychiatry* 1966; 29:398–3
 22. Badin J, Boulain T, Ehrmann S, Skarzynski M, Bretagnol A, Buret J, Benzekri-Lefevre D, Mercier E, Runge I, Garot D, Mathonnet A, Dequin PF, Perrotin D: Relation between mean arterial pressure and renal function in the early phase of shock: A prospective, explorative cohort study. *Crit Care* 2011; 15:R135
 23. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM, Campbell DA Jr: Development and validation of an acute kidney injury risk index for patients undergoing general surgery: Results from a national data set. *ANESTHESIOLOGY* 2009; 110:505–15
 24. Bijker JB, van Klei WA, Vergouwe Y, Eleveld DJ, van Wolfswinkel L, Moons KG, Kalkman CJ: Intraoperative hypotension and 1-year mortality after noncardiac surgery. *ANESTHESIOLOGY* 2009; 111:1217–26
 25. Coriat P, Richer C, Douraki T, Gomez C, Hendricks K, Giudicelli JF, Viars P: Influence of chronic angiotensin-converting enzyme inhibition on anesthetic induction. *ANESTHESIOLOGY* 1994; 81:299–7
 26. Bertrand M, Godet G, Meersschaert K, Brun L, Salcedo E, Coriat P: Should the angiotensin II antagonists be discontinued before surgery? *Anesth Analg* 2001; 92:26–30