Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery

A Retrospective Cohort Analysis

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ABSTRACT

Background: How best to characterize intraoperative hypotension remains unclear. Thus, the authors assessed the relationship between myocardial and kidney injury and intraoperative absolute (mean arterial pressure [MAP]) and relative (reduction from preoperative pressure) MAP thresholds.

Methods: The authors characterized hypotension by the lowest MAP below various absolute and relative thresholds for cumulative 1, 3, 5, or 10 min and also time-weighted average below various absolute or relative MAP thresholds. The authors modeled each relationship using logistic regression. The authors further evaluated whether the relationships between intraoperative hypotension and either myocardial or kidney injury depended on baseline MAP. Finally, the authors compared the strength of associations between absolute and relative thresholds on myocardial and kidney injury using C statistics.

Results: MAP below absolute thresholds of 65 mmHg or relative thresholds of 20% were progressively related to both myocardial and kidney injury. At any given threshold, prolonged exposure was associated with increased odds. There were no clinically important interactions between preoperative blood pressures and the relationship between hypotension and myocardial or kidney injury at intraoperative mean arterial blood pressures less than 65 mmHg. Absolute and relative thresholds had comparable ability to discriminate patients with myocardial or kidney injury from those without.

Conclusions: The associations based on relative thresholds were no stronger than those based on absolute thresholds. Furthermore, there was no clinically important interaction with preoperative pressure. Anesthetic management can thus be based on intraoperative pressures without regard to preoperative pressure. **(ANESTHESIOLOGY 2017; 126:47-65)**

THE perioperative period is characterized by hemodynamic instability. Various degrees of hypotension are common during anesthesia and surgery and may cause organ ischemia. For example, hypotension contributes to oxygen supply–demand mismatch, which appears to be an important cause of postoperative myocardial infarction.[1–3] Furthermore, ischemia and reperfusion may contribute to postoperative acute kidney injury (AKI).[4–10] Myocardial perfusion is dependent on pressure gradient created by diastolic blood pressure[11]; vasomotor responses and regional ischemia in response to decreased blood pressure and cardiac output also contribute to ischemic renal injury.[12,13]

A systematic review of interventions to decrease the incidence of postoperative AKI demonstrated that avoiding hypotension reduced the incidence of AKI.[14] Consistent with the theory that intraoperative hypotension contributes to organ injury, hypotension, defined in various ways, is weakly associated with AKI[8,10] and strongly associated with myocardial infarction[8,15] and death.[9,16]

What We Already Know about This Topic

- Previous studies have demonstrated associations between low mean arterial pressure (MAP) and organ injury, with hypotension defined in terms of minutes or integrated pressures below various absolute thresholds.
- This study assessed the relationship between myocardial and kidney injury and intraoperative absolute (intraoperative MAP) and relative (reduction from preoperative pressure) MAP thresholds using retrospective data from a single institution.

What This Article Tells Us That Is New

- The associations based on relative mean arterial pressure thresholds were no stronger than those based on absolute thresholds. Furthermore, there was no clinically important interaction with preoperative pressure. These data suggest that anesthetic management can thus be based on intraoperative pressures without regard to preoperative pressure.

How best to characterize hypotension remains unclear, and there is no universal definition of hypotension. In a

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systematic review, for example, Bijker *et al.*[17] found 140 definitions for hypotension in 130 articles. A consequence was that the incidence of intraoperative hypotension ranged from 5 to 99% depending on the selected definition.

Several recent studies report associations between low mean arterial pressure (MAP) and organ injury, with hypotension defined in terms of minutes or integrated pressures below various absolute thresholds.[8–10,15] This approach differs from classical anesthesia teaching, which suggests keeping blood pressure within a relative 20% of preoperative values, apparently based on the theory that hypertensive patients require higher than normal pressures to adequately perfuse organs habituated to high pressures. Despite the frequency of this recommendation, it does not appear to be based on credible outcome evidence. Which characterization of blood pressure, absolute *versus* relative hypotension, is most related to organ injury remains unknown.

Therefore, we assessed the relationship between various absolute and relative characterizations of hypotension and myocardial injury after noncardiac surgery (MINS)[18] and AKI in adults having inpatient surgery. Absolute thresholds were characterized by the lowest MAP maintained for various durations and by time under various MAP thresholds. Relative hypotension was characterized by maximum percentage MAP decrease from baseline maintained for various durations and by time under various percentage reductions from baseline. We then evaluated the interaction between preoperative MAP and the relationships between intraoperative hypotension and MINS or AKI. Finally, we determined whether absolute or relative characterizations best predict MINS and AKI.

Materials and Methods

We conducted a retrospective cohort study using data from the Cleveland Clinic Perioperative Health Documentation System and Epic, electronic medical record-based registries of noncardiac surgery patients who had undergone surgery between January 6, 2005, and March 1, 2014, at the Cleveland Clinic, Cleveland, Ohio.

Inclusion criteria were as follows: (1) adults who had inpatient noncardiac surgery between January 6, 2005, and March 1, 2014; (2) preoperative and at least one postoperative serum creatinine measurement available within the first 7 postoperative days; (3) blood pressure recorded in the preanesthesia care evaluation clinic or other preoperative appointments within 6 months before surgery.

Exclusion criteria were as follows: (1) patients with chronic kidney disease defined as preoperative estimated glomerular filtration rate of less than 60 ml × min^{-1} × 1.73 m^{-2} or patients who were on dialysis; (2) urologic procedures including relief of urinary obstruction (International Classification of Diseases, Ninth Revision [ICD-9] codes of 5501, 5502, 5503, 5504, 5511, 5512, 560, 570, 5741, 5749, 602, 6021, 6029, 6096, 6097, 603, 604, 605, 6061, 6062, and 6069), nephrectomy (ICD-9 codes of 554, 5551, 5552, 5553, and 5554), or renal transplantation (ICD-9 codes of 5561 and 5569); (3) patients who had anesthesia for less than 60 min or missing baseline variables; (4) patients with invalid or unavailable data for more than 10 consecutive minutes.

Outcomes

1. MINS was defined as at least one increased postoperative value of either fourth-generation troponin T or creatine kinase-MB above the upper limit of normal in the 7 days after operation. The upper limit of normal was defined as 0.03 ng/ml for troponin T[18] and 8.8 ng/ml for creatine kinase-MB.[3] Eligible patients without postoperative cardiac enzyme determinations were assumed not to have acute myocardial injury.
2. Postoperative AKI was defined by increases in serum creatinine between preoperative and postoperative values. Preoperative creatinine was taken to be the last before surgery. Postoperative creatinine was taken to be the highest concentration measured within 7 postoperative days. According to the Acute Kidney Injury Network definition, patients were considered to have AKI if the postoperative value was either more than 1.5-fold or more than 0.3 mg/dl before surgery.[8]

Statistical Methods

MAP and Artifact Removing Algorithm. Intraoperative MAPs recorded in the Perioperative Health Documentation System cannot be modified by clinicians, but can be identified as artifactual. Invasive pressures were recorded at 1-min intervals; noninvasive pressures were recorded at 1- to 5-min intervals. We removed artifacts using the following rules, in order: (1) blood pressures documented as artifacts; (2) pressures out-of-range defined by (a) SBP greater than or equal to 300 or SBP less than or equal to 20 mmHg, (b) SBP less than or equal to DBP + 5 mmHg, or (c) DBP less than or equal to 5 mmHg or DBP greater than or equal to 225 mmHg; (3) abrupt changes defined by SBP change greater than or equal to 80 mmHg within 1 min in either direction or abrupt SBP changes greater than or equal to 40 mmHg within 2 min in both directions. Pressures between measurements were linearly interpolated.

Baseline MAP is described as the average of all MAP readings in the 6 months before surgery, excluding measurements during a hospital stay. Anesthesia time was defined as the interval between induction and emergence.

Confounding Variables. Potentially confounding variables are listed in table 1. We defined preexisting medical conditions using ICD-9 billing codes and included only those fulfilling at least one of the following: (1) appeared in the patient "problem list" with a date preceding the date of surgery; (2) appeared in an ICD-9 list before the index surgery; or (3) were flagged as a chronic ICD-9 condition based on Healthcare Cost and Utilization Project definitions. Because there were many types of surgical procedures, we characterized

Table 1. Patient Baseline and Intraoperative Characteristics by Postoperative AKI and MINS

Factors	MINS (n = 1,760)	Non-MINS (n = 55,555)	*P* Values*	AKI (n = 3,215)	Non-AKI (n = 54,100)	*P* Values*
Female (%)	708 (40)	31,234 (56)	< 0.001	1,211 (38)	30,731 (57)	< 0.001
Race (%)			0.72			< 0.001
White	1,530 (87)	48,077 (87)		2,649 (82)	46,958 (87)	
Black	207 (12)	6,825 (12)		523 (16)	6,509 (12)	
Other	23 (1)	653 (1)		43 (1)	633 (1)	
Age, yr	67 ± 13	56 ± 15	< 0.001	61 ± 15	56 ± 16	< 0.001
Emergency (%)	257 (15)	1,817 (3)	< 0.001	311 (10)	1,763 (3)	< 0.001
ASA physical status (%)			< 0.001			< 0.001
1	7 (0)	1,217 (2)		21 (1)	1,203 (2)	
2	187 (11)	21,422 (39)		645 (20)	20,964 (39)	
3	1,023 (58)	29,290 (53)		1,887 (59)	28,426 (53)	
4	527 (30)	3,592 (6)		648 (20)	3,471 (6)	
5	16 (1)	34 (0)		14 (0)	36 (0)	
Use of arterial catheter (%)	1,411 (80)	21,729 (39)	< 0.001	1,892 (59)	21,248 (39)	< 0.001
Previous medical history						
Congestive heart failure	338 (19)	2,096 (4)	< 0.001	362 (11)	2,072 (4)	< 0.001
Valvular disease	195 (11)	2,345 (4)	< 0.001	236 (7)	2,304 (4)	< 0.001
Pulmonary circulation disease	101 (6)	979 (2)	< 0.001	121 (4)	959 (2)	< 0.001
Peripheral vascular disease	544 (31)	4,033 (7)	< 0.001	520 (16)	4,057 (8)	< 0.001
Hypertension	1,287 (73)	26,670 (48)	< 0.001	2,062 (64)	25,895 (48)	< 0.001
Paralysis	114 (6)	1,440 (3)	< 0.001	93 (3)	1,461 (3)	0.51
Other neurologic disorders	191 (11)	4,368 (8)	< 0.001	206 (6)	4,353 (8)	< 0.001
Chronic pulmonary disease	430 (24)	8,041 (14)	< 0.001	629 (20)	7,842 (15)	< 0.001
Diabetes	464 (26)	9,027 (16)	< 0.001	889 (28)	8,602 (16)	< 0.001
Hypothyroidism	215 (12)	6,615 (12)	0.69	385 (12)	6,445 (12)	0.92
Renal failure	79 (4)	542 (1)	< 0.001	136 (4)	485 (1)	< 0.001
Liver disease	151 (9)	3,039 (5)	< 0.001	396 (12)	2,794 (5)	< 0.001
Lymphoma	39 (2)	1,037 (2)	0.29	62 (2)	1,014 (2)	0.83
Metastatic cancer	156 (9)	4,191 (8)	0.040	334 (10)	4013 (7)	< 0.001
Solid tumor without metastasis	296 (17)	8,139 (15)	0.012	712 (22)	7,723 (14)	< 0.001
Rheumatoid arthritis/collagen vas	96 (5)	2,222 (4)	0.002	117 (4)	2,201 (4)	0.23
Coagulopthy	395 (22)	2,739 (5)	< 0.001	582 (18)	2,552 (5)	< 0.001
Obesity	397 (23)	13,183 (24)	0.25	940 (29)	12,640 (23)	< 0.001
Weight loss	326 (19)	3,345 (6)	< 0.001	634 (20)	3,037 (6)	< 0.001
Fluid and electrolyte disorders	95 (5)	2,109 (4)	< 0.001	190 (6)	2,014 (4)	< 0.001
Chronic blood loss anemia	109 (6)	1,054 (2)	< 0.001	142 (4)	1,021 (2)	< 0.001
Deficiency anemias	139 (8)	3,083 (6)	< 0.001	293 (9)	2,929 (5)	< 0.001
Alcohol abuse	83 (5)	1,222 (2)	< 0.001	175 (5)	1,130 (2)	< 0.001
Drug abuse	38 (2)	796 (1)	0.012	71 (2)	763 (1)	< 0.001
Psychoses	89 (5)	2,079 (4)	0.004	161 (5)	2,007 (4)	< 0.001
Depression	234 (13)	8,550 (15)	0.016	446 (14)	8,338 (15)	0.019
Cardiac medication history, n (%)						
ACE inhibitor	928 (53)	18,596 (33)	< 0.001	1,442 (45)	18,082 (33)	< 0.001
β-blocker	318 (18)	5,596 (10)	< 0.001	504 (16)	5,410 (10)	< 0.001
CA blocker	414 (24)	8,050 (14)	< 0.001	694 (22)	7,770 (14)	< 0.001
Diuretic	915 (52)	17,720 (32)	< 0.001	1,527 (48)	17,108 (32)	< 0.001
Angiotensin receptor blockers	291 (17)	5,928 (11)	< 0.001	513 (16)	5,706 (11)	< 0.001
Preoperative						
Preoperative hemoglobin, g/dl	12.7 ± 2.1	13.3 ± 1.8	< 0.001	12.6 ± 2.1	13.3 ± 1.8	< 0.001
Preoperative creatinine	0.9 ± 0.2	0.8 ± 0.2	< 0.001	0.9 ± 0.2	0.8 ± 0.2	< 0.001
Baseline EGFR, ml · min · 1.73 m^{-2}	94 ± 32	97 ± 28	< 0.001	98 ± 36	96 ± 28	0.016
Baseline MAP	92 ± 10	93 ± 10	0.12	94 ± 10	92 ± 9	< 0.001
Intraoperative						
Surgical time, h	5.1 ± 2.8	3.7 ± 2.0	< 0.001	4.7 ± 2.6	3.7 ± 2.0	< 0.001
Blood loss, cc	350 [100, 1,100]	150 [50, 300]	< 0.001	300 [100, 700]	150 [50, 300]	< 0.001

(*Continued*)

Table 1. (Continued)

Factors	MINS (n = 1,760)	Non-MINS (n = 55,555)	*P* Values*	AKI (n = 3,215)	Non-AKI (n = 54,100)	*P* Values*
Top 10 surgical procedure, n (%)			< 0.001			< 0.001
Colorectal resection	84 (5)	4,795 (9)		414 (13)	4,465 (8)	
Arthroplasty knee	38 (2)	4,213 (8)		196 (6)	4,055 (8)	
Hysterectomy; abdominal and vaginal	20 (1)	3,390 (6)		86 (3)	3,324 (6)	
Spinal fusion	225 (13)	3,092 (6)		82 (3)	3,235 (6)	
Hip replacement	96 (5)	3,162 (6)		169 (5)	3,089 (6)	
Other OR upper GI therapeutic procedures	34 (2)	3,135 (6)		92 (3)	3,077 (6)	
Other OR lower GI therapeutic procedures	41 (2)	2,601 (5)		195 (6)	2,447 (5)	
Incision and excision of CNS	61 (3)	2,298 (4)		36 (1)	2,323 (4)	
Other OR GI therapeutic procedures	90 (5)	2,205 (4)		173 (5)	2,122 (4)	
Other OR therapeutic nervous system procedures	61 (3)	2,298 (4)		28 (1)	1,932 (4)	

Data are presented as mean ± SD, median [25th, 75th percentiles] or n (%).

*P values from chi-square test, Student's *t* test, or Wilcoxon rank sum test, as appropriate.

ACE = angiotensin-converting enzyme; AKI = acute kidney injury; ASA = American Society of Anesthesiologists; CA = calcium channel; EGFR = estimated glomerular filtration rate; GI = gastrointestinal; MAP = mean arterial pressure; MINS = myocardial injury after noncardiac surgery; OR = operating room.

each procedure code into one of 231 clinically meaningful categories using the Agency for Healthcare Research and Quality's Clinical Classifications Software for Services and Procedures.[19] We then aggregated low-frequency event or nonevent categories (n < 10) into one group and used that as the reference group (a low-risk group).[20]

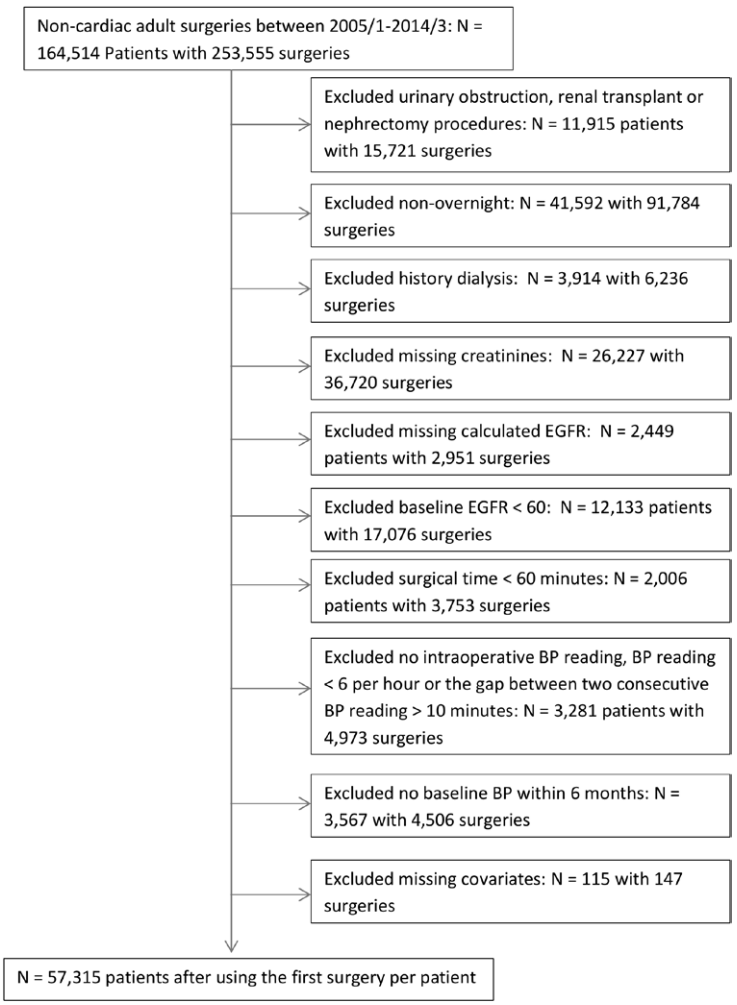

Fig. 1. Flow chart. BP = blood pressure; EGFR = estimated glomerular filtration rate.

Table 2. Univariable Relationship between MAP Exposures and Outcomes

Exposures	MINS (n = 1,760)	Non-MINS (n = 55,555)	*P* Values*	AKI (n = 3,215)	Non-AKI (n = 54,100)	*P* Values*
Baseline MAP	92 ± 10	93 ± 10	0.12	94 ± 10	92 ± 9	< 0.001
Preinduction MAP	102 ± 18	101 ± 16	0.12	102 ± 17	101 ± 16	0.002
Intraoperative TWA-MAP	83 ± 10	84 ± 10	< 0.001	84 ± 10	84 ± 10	0.11
Lowest MAP, mmHg, for cumulative minutes						
≥ 1	53 ± 13	59 ± 11	< 0.001	56 ± 12	59 ± 11	< 0.001
≥ 3	58 ± 11	63 ± 10	< 0.001	60 ± 11	63 ± 10	< 0.001
≥ 5	60 ± 10	65 ± 9	< 0.001	62 ± 10	65 ± 9	< 0.001
≥ 10	63 ± 10	68 ± 9	< 0.001	65 ± 10	68 ± 9	< 0.001
Lowest % MAP decrease from baseline (%) for cumulative minutes,%						
≥ 1	42 ± 15	36 ± 13	< 0.001	40 ± 14	36 ± 13	< 0.001
≥ 3	37 ± 14	31 ± 12	< 0.001	35 ± 12	31 ± 12	< 0.001
≥ 5	34 ± 13	30 ± 11	< 0.001	33 ± 12	29 ± 12	< 0.001
≥ 10	31 ± 13	27 ± 11	< 0.001	30 ± 12	26 ± 11	< 0.001
Lowest MAP (mmHg) for sustained minutes						
≥ 1	53 ± 13	59 ± 11	< 0.001	56 ± 12	59 ± 11	< 0.001
≥ 3	61 ± 11	65 ± 9	< 0.001	62 ± 10	65 ± 9	< 0.001
≥ 5	64 ± 10	67 ± 9	< 0.001	65 ± 10	67 ± 9	< 0.001
≥ 10	70 ± 10	71 ± 9	< 0.001	70 ± 10	72 ± 9	< 0.001
Lowest % MAP decrease from baseline for sustained minutes, %						
≥ 1	42 ± 15	36 ± 13	< 0.001	40 ± 14	36 ± 13	< 0.001
≥ 3	33 ± 13	30 ± 11	< 0.001	33 ± 12	30 ± 11	< 0.001
≥ 5	30 ± 13	27 ± 11	< 0.001	30 ± 12	27 ± 11	< 0.001
≥ 10	24 ± 13	-22 ± 11	< 0.001	25 ± 12	22 ± 11	< 0.001
Minutes for MAP, mmHg						
< 75	67 [27, 139]	40 [15, 85]	< 0.001	54 [21, 114]	40 [15, 85]	< 0.001
< 70	36 [12, 80]	18 [4, 46]	< 0.001	27 [8, 67]	18 [4, 46]	< 0.001
< 65	15 [4, 39]	6 [0, 19]	< 0.001	10 [2, 32]	6 [0, 19]	< 0.001
< 60	5 [0, 16]	1 [0, 6]	< 0.001	3 [0, 12]	1 [0, 6]	< 0.001
< 55	1 [0, 6]	0 [0, 1]	< 0.001	0 [0, 4]	0 [0, 1]	< 0.001
< 50	0 [0, 2]	0 [0, 0]	< 0.001	0 [0, 1]	0 [0, 0]	< 0.001
Minutes for % MAP decrease from baseline						
< 20	57 [18, 127]	33 [9, 81]	< 0.001	50 [16, 113]	32 [9, 80]	< 0.001
< 30	13 [2, 42]	5 [0, 21]	< 0.001	10 [1, 36]	5 [0, 21]	< 0.001
< 40	1 [0, 7]	0 [0, 2]	< 0.001	0 [0, 6]	0 [0, 2]	< 0.001
< 50	0 [0, 1]	0 [0, 0]	< 0.001	0 [0, 0]	0 [0, 0]	< 0.001
TWA under MAP, mmHg						
< 75	1.9 [0.7, 4.0]	1.3 [0.4, 3.0]	< 0.001	1.6 [0.5, 3.5]	1.3 [0.4, 3.1]	< 0.001
< 70	0.9 [0.3, 2.0]	0.5 [0.1, 1.3]	< 0.001	0.6 [0.1, 1.6]	0.5 [0.1, 1.3]	< 0.001
< 65	0.3 [0.1, 0.9]	0.1 [0.0, 0.5]	< 0.001	0.2 [0.0, 0.6]	0.1 [0.0, 0.5]	< 0.001
< 60	0.1 [0.0, 0.3]	0.0 [0.0, 0.1]	< 0.001	0.0 [0.0, 0.2]	0.0 [0.0, 0.1]	< 0.001
< 55	0.0 [0.0, 0.1]	0.0 [0.0, 0.0]	< 0.001	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	< 0.001
TWA under % MAP decrease from baseline, mmHg						
< 10	5.5 [2.3, 10.7]	4.6 [1.8, 9.2]	< 0.001	5.2 [2.2, 10.0]	4.5 [1.7, 9.0]	< 0.001
< 15	3.1 [1.1, 7.1]	2.4 [0.7, 5.7]	< 0.001	2.9 [1.0, 6.5]	2.4 [0.7, 5.6]	< 0.001
< 20	1.6 [0.5, 4.1]	1.1 [0.2, 3.1]	< 0.001	1.4 [0.4, 3.7]	1.0 [0.2, 3.0]	< 0.001
< 25	0.7 [0.1, 2.2]	0.4 [0.0, 1.4]	< 0.001	0.6 [0.1, 1.9]	0.4 [0.0, 1.4]	< 0.001
< 30	0.3 [0.0, 1.0]	0.1 [0.0, 0.6]	< 0.001	0.2 [0.0, 0.8]	0.1 [0.0, 0.5]	< 0.001
AUC under MAP, mmHg * min						
< 75	520 [178, 1,104]	258 [73, 617]	< 0.001	383 [120, 908]	258 [73, 617]	< 0.001
< 70	227 [63, 559]	91 [13, 269]	< 0.001	152 [33, 439]	92 [13, 269]	< 0.001
< 65	85 [14, 242]	21 [0, 97]	< 0.001	46 [3, 177]	21 [0, 97]	< 0.001
< 60	23 [0, 89]	1 [0, 26]	< 0.001	9 [0, 57]	1 [0, 26]	< 0.001
< 55	3 [0, 30]	0 [0, 4]	< 0.001	0 [0, 14]	0 [0, 4]	< 0.001

(*Continued*)

Table 2. (Continued)

Exposures	MINS (n = 1,760)	Non-MINS (n = 55,555)	*P* Values*	AKI (n = 3,215)	Non-AKI (n = 54,100)	*P* Values*
AUC under % MAP decrease from baseline, % * min						
< 10	1,449 [544, 3,015]	861 [318, 1,868]	< 0.001	1,275 [472, 2,692]	855 [315, 1,860]	< 0.001
< 15	850 [271, 1,970]	462 [134, 1,165]	< 0.001	719 [233, 1,718]	458 [132, 1,158]	< 0.001
< 20	437 [116, 1,146]	212 [39, 634]	< 0.001	356 [91, 998]	210 [39, 630]	< 0.001
< 25	199 [37, 597]	77 [5, 297]	< 0.001	151 [25, 507]	76 [5, 295]	< 0.001
< 30	80 [7, 271]	19 [0, 116]	< 0.001	51 [2, 226]	19 [0, 116]	< 0.001

Data are presented as mean ± SD, median [25th, 75th percentiles] or n (%).

*P values from chi-square test, Student's *t* test, or Wilcoxon rank sum test.

AKI = acute kidney injury; AUC = area under curve; MAP = mean arterial pressure; MINS = myocardial injury after noncardiac surgery; TWA = time-weighted average.

Determining MAP Thresholds. We first determined the absolute and relative (percent below baseline) thresholds below which MINS and AKI began to increase. Specifically, we assessed the relationships between MINS or AKI and the lowest MAP or the lowest percent decrease from baseline for a cumulative case total of 1, 3, 5, and 10 min, and time-weighted average under absolute thresholds (*i.e.*, less than 55, less than 60, less than 65, less than 70, less than 75 mmHg) or relative thresholds (i.e.,

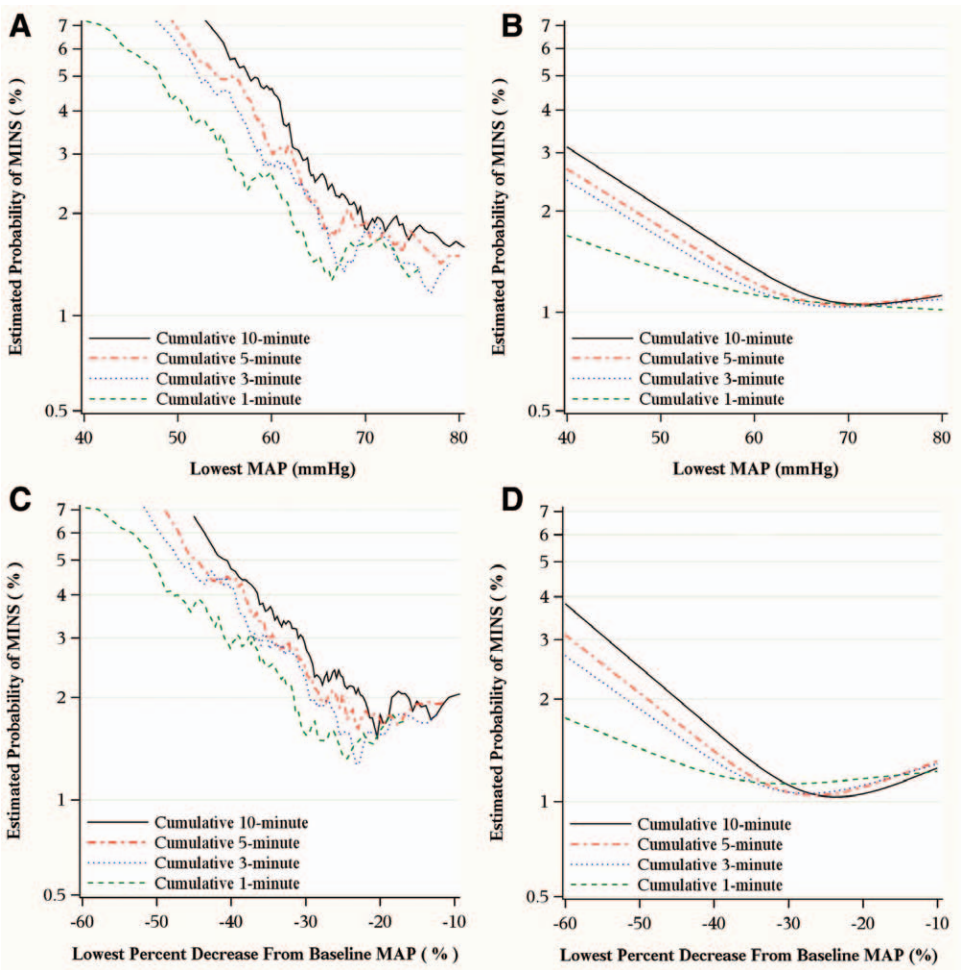

Fig. 2. Lowest mean arterial pressure (MAP) thresholds for myocardial injury after noncardiac surgery (MINS). Univariable and multivariable relationship between MINS and absolute and relative lowest MAP thresholds. (*A*) and (*C*) Estimated probability of MINS were from the univariable moving-window with the width of 10% data; (*B*) and (*D*) were from multivariable logistic regression smoothed by restricted cubic spline with three degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. Multivariable models adjusted for covariates in table 1. (*A*) and (*B*) show that there was a change point (*i.e.*, decreases steeply up and then flattens) around 65 mmHg, but 20% was not a change point from (*C*) and (*D*).

greater than 10%, greater than 15%, greater than 20%, greater than 25%, greater than 30% decrease from baseline).

We first assessed the univariable relationship between each MAP threshold and MINS and AKI using moving-average smoothing plots. Relationships were then studied further using multivariable logistic regression to adjust for confounding and model the relationships; linearity between each MAP exposure and response was modeled by a restricted cubic spline function with three knots located at 10th, 50th, and 90th percentiles. The univariable moving-average plots and multivariable smoothed cubic spline curves were studied to find optimal thresholds based on the data. We further evaluated interactions between baseline MAP and the relationship between exposure and outcome.

Deriving MAP Exposures. Based on inspection of exposure *versus* outcome curves, we determined that absolute thresholds of 65 mmHg and lower and relative thresholds of 20% or more decrease from the baseline MAP were associated with the increased risk of both MINS and AKI. We then defined our main absolute and relative exposures to be (1) number of minutes under each threshold and (2) area under each threshold. Since all relationships were found to be nonlinear, we categorized patients as belonging to either a reference group who spent no time under a given threshold or to one of four groups based on quartiles of nonzero time spent under the threshold.

Specifically, we defined the absolute MAP reference group as patients whose intraoperative MAPs were never less than 65 mmHg. For the remaining patients, we counted the number of minutes within the lowest achieved category per patient: less than 50, 50 to 55, 55 to 60, and 60 to 65 mmHg. That is, each patient was assigned uniquely to one of the four hypotension categories. We then categorized cumulative minutes of exposure into 1, 2 to 4, or greater than equal to 5 min for a total of 12 groups (*i.e.*, four pressure ranges by three durations) and compared each to the reference group.

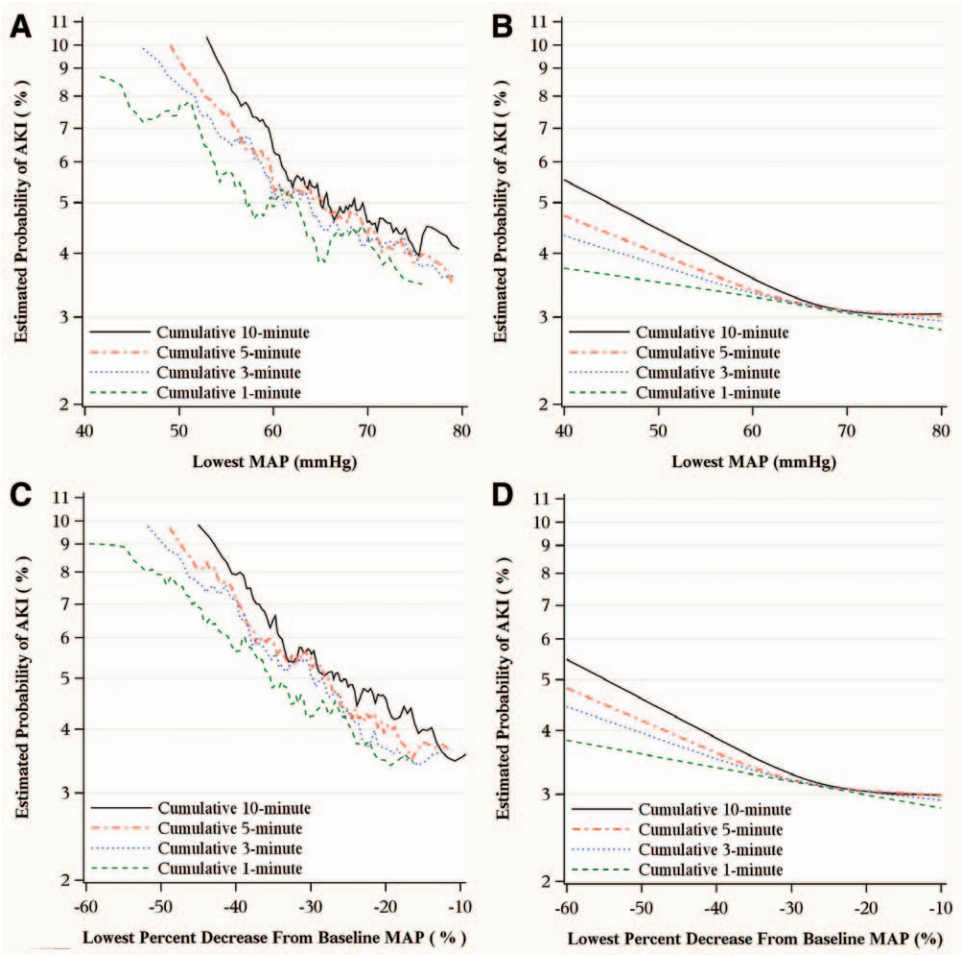

Fig. 3. The lowest mean arterial pressure (MAP) thresholds for acute kidney injury (AKI). Univariable and multivariable relationship between AKI and absolute and relative lowest MAP thresholds. (*A*) and (*C*) Estimated probability of AKI were from the univariable moving-window with the width of 10% data; (*B*) and (*D*) were from multivariable logistic regression smoothed by restricted cubic spline with three degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. Multivariable models adjusted for covariates in table 1. (*A*) and (*B*) show that there was a change point (*i.e.*, decreases steeply up and then flattens) around 65 mmHg, but 20% was not a change point from (*C*) and (*D*).

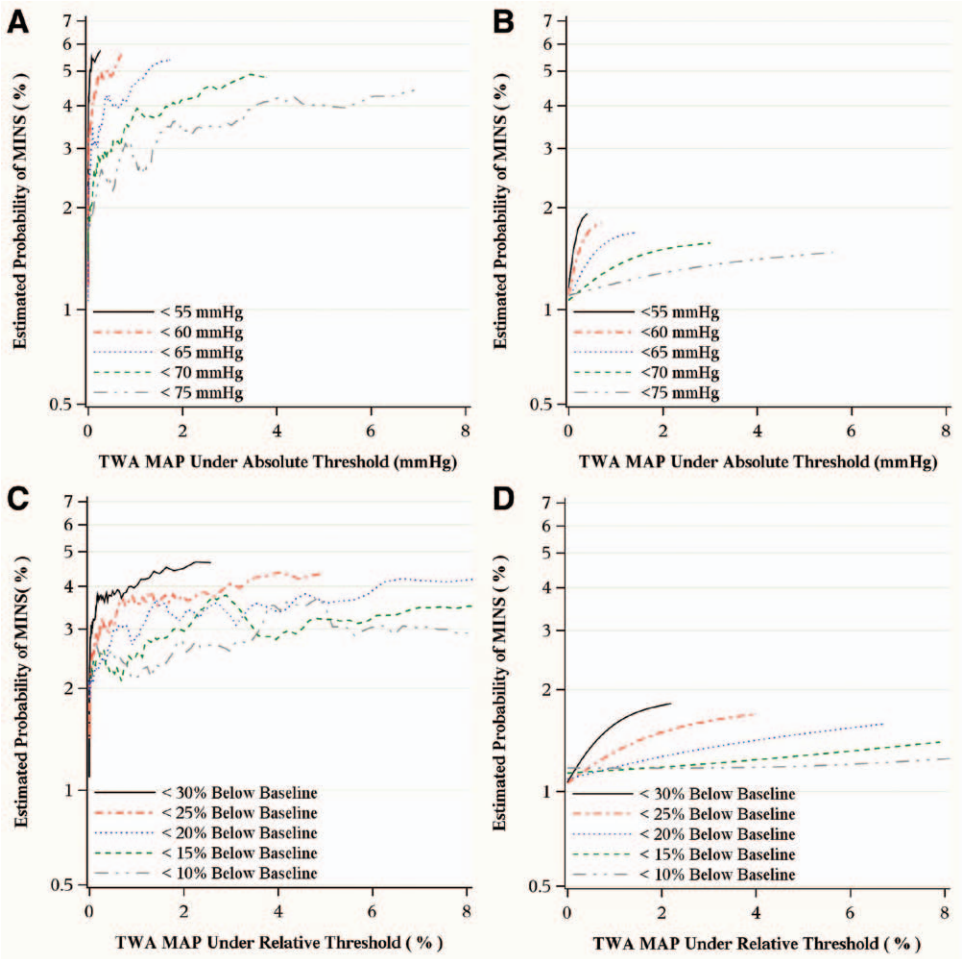

Fig. 4. Time-weighted average (TWA) mean arterial pressure (MAP) under absolute and relative thresholds for myocardial injury after noncardiac surgery (MINS). Univariable and multivariable relationship between MINS and TWA MAP under absolute and relative thresholds. (*A*) and (*C*) Estimated probability of MINS were from the univariable moving-window with the width of 10% data; (*B*) and (*D*) were from multivariable logistic regression smoothed by restricted cubic spline with three degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. Multivariable models adjusted for covariates in table 1. (*A*) and (*B*) show that MAP less than 65 mmHg was a change point since the risk of MINS was starting to increase more compared to the thresholds of 70 and 75 mmHg, but 20% was not a change point from (*C*) and (*D*).

We similarly defined the relative MAP reference group as patients whose intraoperative MAPs were never more than 20% below the preoperative reference pressure. For the remaining patients, we counted the number of minutes within the lowest achieved category per patient: 20 to 30%, 30 to 40%, 40 to 50%, and greater than 50% below baseline. Thus, each patient was again assigned uniquely to one of 12 groups (*i.e.*, four pressure ranges by three durations) and compared each to the reference group.

Multivariable logistic regression was used to assess the association between the above MAP exposures and postoperative MINS or AKI. All potentially confounding variables listed in table 1 were forced into the models regardless of statistical significance. Bonferroni correction was used to adjust for four main comparisons within each exposure of interest, with $P < 0.0125$ (*i.e.*, $P < 0.05/4 = 0.0125$) considered statistically significant. Interactions between baseline MAP and exposures were considered significant if $P < 0.05$. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute, USA).

Sample Size Considerations. We expected to have between 50,000 and 150,000 patients meeting all study criteria. With at least 50,000 patients and the incidence of MINS or AKI of 2% or more, we had good statistical power (80% or more) to detect moderately small odds ratios, especially given the continuous/ordinal nature of the predictor variables.

Results

Of 164,514 patients having noncardiac surgery between 2005 and 2015, analysis included 57,315 patients who met our inclusion and exclusion criteria (fig. 1). Different subsets of these patients were included in studies by Walsh *et al.*[8] and Mascha *et al.*[16] The overall incidence of MINS was 3.1% and of AKI was 5.6% among qualified patients. Only 8,558

patients (15%) had postoperative troponin tests, and we assumed that patients without the test did not have MINS.

Nearly all demographic, medical history, procedural, medicine, preoperative, and intraoperative factors were associated with both MINS and AKI (table 1). Descriptive statistics for baseline MAP and all MAP exposures are displayed in table A1. Baseline MAP was based on a mean of 5 ± 3 values per patient in the 6 months before surgery. Average baseline MAP was 93 ± 10 mmHg; preinduction MAP averaged 101 ± 16 mmHg, and intraoperative time-weighted average MAP was 84 ± 10 mmHg.

Univariable analyses showed that patients having postoperative MINS or AKI had higher time-weighted average, area under threshold, and number of minutes under all thresholds compared to those with no evidence of AKI or MINS (all $P < 0.001$; table 2).

Univariable moving-average and multivariable spline smoothing plots for the lowest observed MAPs for a patient are shown for MINS in fig. 2 and for AKI in fig. 3. Odds for both MINS and AKI increased for decreasing thresholds of MAP less than 65 mmHg for any of 1, 3, 5, or 10 min. A relative MAP threshold of 20% below baseline was not an obvious change-point for AKI (fig. 3), but it was for MINS (fig. 2). We thus selected an absolute reference threshold of 65 mmHg and a relative reference threshold of 20% below baseline for further analysis.

Increasing time-weighted average MAP under various absolute and relative thresholds was associated with increased odds of MINS (fig. 4) and AKI (fig. 5), both univariably and multivariably. Further, the relationships strengthened at lower thresholds. For example, the observed slope for less than 60 mmHg is steeper than that for less than 65 mmHg, and the

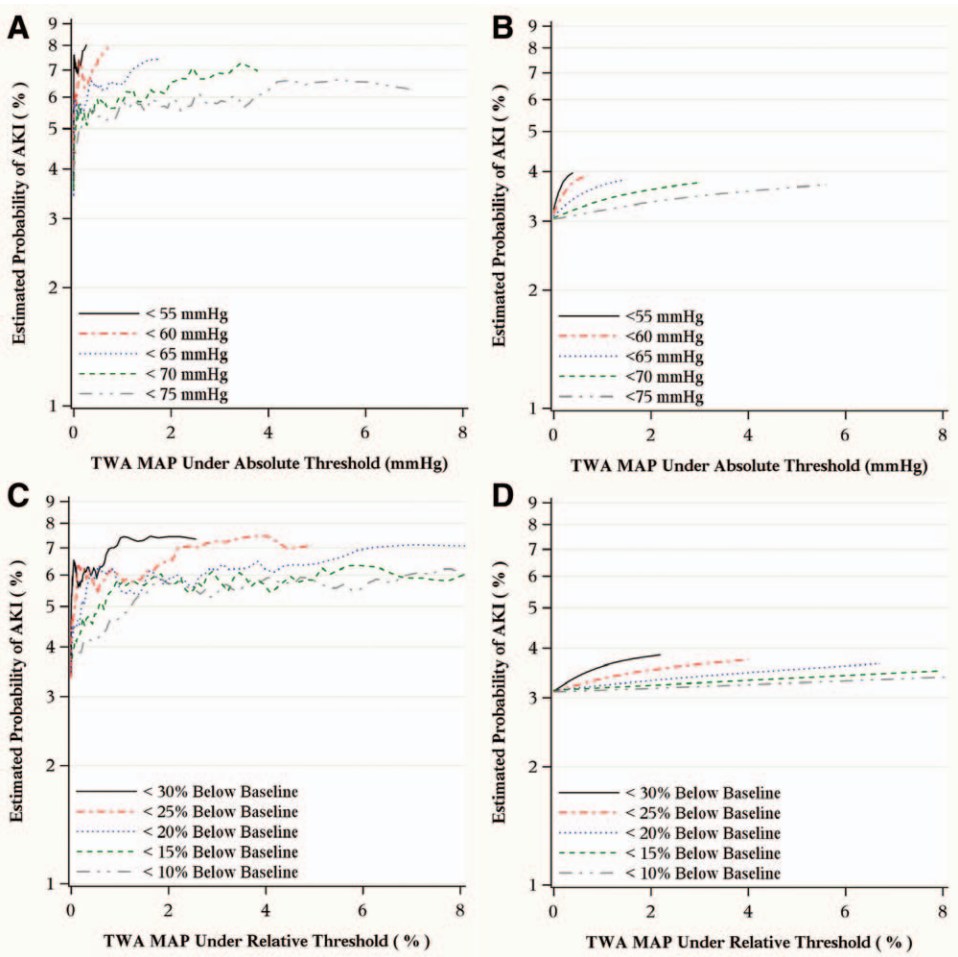

Fig. 5. Time-weighted average (TWA) mean arterial pressure (MAP) under absolute and relative thresholds for acute kidney injury (AKI). Univariable and multivariable relationship between AKI and TWA MAP under absolute and relative thresholds. (*A*) and (*C*) Estimated probability of AKI were from the univariable moving-window with the width of 10% data; (*B*) and (*D*) were from multivariable logistic regression smoothed by restricted cubic spline with three degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. Multivariable models adjusted for covariates in table 1. (*A*) and (*B*) show that MAP less than 65 mmHg was a change point since the risk of AKI was starting to increase more compared to the thresholds of 70 and 75 mmHg, but 20% was not a change point from (*C*) and (*D*).

Table 3. Interaction *P* Values between Baseline MAP and Postoperative AKI and MINS*

Exposure	MINS	AKI
Lowest MAP for cumulative minutes		
≥ 1	0.19	0.94
≥ 3	0.012	0.99
≥ 5	0.001	0.64
≥ 10	< 0.001	0.38
Lowest % MAP decrease for cumulative minutes		
≥ 1	0.52	0.50
≥ 3	0.92	0.42
≥ 5	0.84	0.23
≥ 10	0.66	0.10
TWA under MAP, mmHg		
< 75	0.012	0.80
< 70	0.029	0.66
< 65	0.048	0.48
< 60	0.10	0.70
< 55	0.083	0.95
TWA under % MAP decrease from baseline		
< 10	0.67	0.38
< 15	0.64	0.53
< 20	0.69	0.68
< 25	0.93	0.72
< 30	0.91	0.52

*P values from multivariable logistic regression adjusting for covariates listed in table 1.

AKI = acute kidney injury; MAP = mean arterial pressure; MINS = myocardial injury after noncardiac surgery; TWA = time-weighted average.

observed slope for less than 25% below baseline is steeper than that for pressures less than 20% below baseline (figs. 4 and 5).

There was no interaction between baseline MAP and the relationship between the TWA under various relative thresholds for either MINS or AKI. Furthermore, there was no interaction with TWA under absolute thresholds for AKI (all $P > 0.40$). There was some evidence of interaction between baseline MAP and the relationship between TWA under absolute thresholds and MINS (table 3). Investigating further, univariable moving-average and multivariable spline smoothing plots by quartile of baseline MAP showed that there were no clinically important interactions at MAPs less than 65 mmHg (fig. 6).

Discriminative Ability

Using different absolute or relative thresholds did not increase discriminative ability, as evidenced by similar C-statistic values. The full multivariable model for MINS (table A2), including all baseline and intraoperative covariables mentioned in table 1, has a C statistic of 0.86. In contrast, blood pressure alone had a C statistic between 0.55 and 0.66. Whether hypotension exposure was defined by cumulative minutes of the lowest MAP (0.62 to 0.65) or duration under various thresholds (0.55 to 0.62), the C statistic values were essentially the same for absolute and relative exposures. There was thus no advantage to using relative thresholds for myocardial injury.

For AKI, the full multivariable model, including all baseline and intraoperative covariables mentioned in table 1, had a C statistic of 0.81 (table A3). In contrast, blood pressure alone had a C statistic between 0.54 and 0.59. Whether hypotension exposure was defined by cumulative minutes of lowest MAP or duration under various thresholds, the C statistic was nearly identical for absolute and relative thresholds. There was thus no advantage to using relative thresholds for AKI either.

Relationship between Exposure Categories and Outcomes

Time spent under the absolute threshold of MAP less than 65 mmHg had increased odds of MINS, with an odds ratio (OR; 98.75% CI) of 1.34 (1.06 to 1.68) for the third quartile and 1.60 (1.28 to 2.01) for the fourth quartile (table 4). Results were similar when hypotension exposure was characterized by area (rather than minutes) under absolute thresholds. In contrast, there were no significant associations between minutes or area under the relative threshold of 20% below baseline and MINS. Hypotension exposure was also characterized by various blood pressure ranges and exposure durations within each range. For instance, MAP less than 50 mmHg for at least 1 min or a 50% decrease from baseline for at least 1 min increased the odds of MINS after Bonferroni correction.

Time spent under the absolute threshold of MAP less than 65 mmHg had increased odds of AKI compared to patients never going less than 65 mmHg, with an OR (98.75% CI) of 1.20 (1.02 to 1.40) for the third quartile and 1.35 (1.14 to 1.58) for the fourth quartile (table 5). When hypotension exposure was characterized by area (rather than time) under absolute thresholds, odds were higher than reference only for the fourth quartile, with OR (98.75% CI) of 1.34 (1.15 to 1.58). For a relative threshold of 20% below baseline, again the fourth quartile had significantly higher odds of AKI with OR (98.75% CI) of 1.27 (1.01 to 1.61). The lowest hypotension exposure was also characterized by various blood pressure ranges and by exposure durations within each range. For instance, absolute categories of 50 to 55 mmHg for at least 1 min and less than 50 mmHg had higher odds of AKI compared to those never less than 65 mmHg. A relative decrease of greater than 50% from baseline MAP had higher odds of AKI compared to those never reaching less than 20% of baseline.

Discussion

We first characterized hypotension exposure by the lowest MAP maintained for various durations and by time under various *absolute* MAP thresholds. MAP less than 65 mmHg for greater than equal to 13 min (characterizing 50% of the patients who ever went less than 65 mmHg) was associated with significantly higher odds of myocardial and kidney injury. Injury was more common at lower absolute thresholds, and when hypotension was prolonged. At a MAP of 50 mmHg, for example, just 1 min significantly increased the risk for both myocardial and kidney injury.

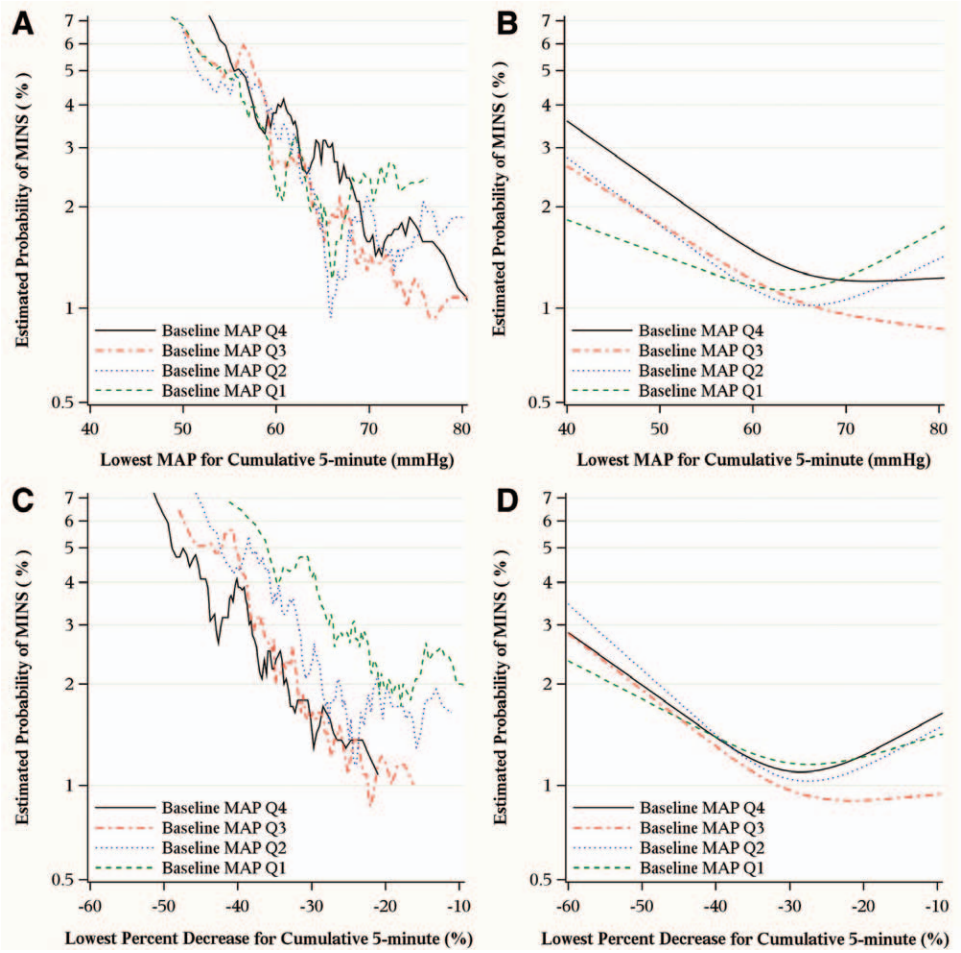

Fig. 6. Interaction between effects on myocardial injury after noncardiac surgery (MINS). (*A*) and (*C*) Estimated probability of MINS were from the univariable moving-window with the width of 10% data; (*B*) and (*D*) were from multivariable logistic regression smoothed by restricted cubic spline with three degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. Multivariable models adjusted for covariates in table 1. The interaction *P* values between the lowest mean arterial pressure (MAP) and baseline were < 0.001 and 0.84 between the lowest % MAP decrease and baseline, respectively. However, (*A*) and (*B*) plots show that there were no strong interaction effects as long as MAP is less than 65 mmHg.

Our results are broadly consistent with the results of previous reports. Based on previous studies, MAP less than absolute thresholds of 49 to 60 for various durations ranging from 1 to 30 min increases the risk of myocardial and kidney injury and mortality.[8–10,15,16] Available analyses thus suggest that even short periods of hypotension below MAPs thresholds of 50 to 65 mmHg are associated with kidney and myocardial injury. While causality cannot be determined from analysis of purely observational data, all results suggest that anesthesiologists should avoid unnecessary hypotension. In this context, it is sobering that therapeutic hypotension was used for decades—often for nonessential reasons.

We also characterized hypotension exposure by time under various *relative* MAP thresholds. Injury was more common at lower absolute thresholds, and when hypotension was prolonged. For example, a cumulative time exceeding 90 min (highest quartile of patients) with MAP less than 20% below preoperative values was needed to increase the odds of kidney injury, and total minutes less than 20% was not significant for myocardial injury. When MAP was more than 50% below preoperative values, just 5 min significantly increased the risk for both myocardial and kidney injury.

Again, our results are broadly consistent with the results of previous reports. Monk *et al.*[9] showed that blood pressure measurements less than 50% below baseline was associated with increased 30-day mortality although their analysis was limited in that one third of their patients lacked baseline blood pressures. Van Waes *et al.*[15] showed that a relative decrease in MAP to values less than 40% below preinduction blood pressure for more than 30 min was associated with the increased incidence of myocardial injury. Available analyses thus suggest that sufficient time with pressures less than 20% or even short periods of hypotension to less than 40 to 50% below preoperative MAPs are associated with kidney and myocardial injury. The classical teaching that intraoperative pressures should be maintained within 20% of preoperative values thus appears justified.

The interaction between preoperative blood pressure and the relationship between intraoperative blood pressure and

Table 4. MINS: Multivariable Association with Absolute and Relative MAP Thresholds

Threshold	Total (n = 57,315)	MINS (n = 1,760)	Adjusted OR (98.75% CI)*	*P* Values*
Time under MAP < 65 mmHg				< 0.001
Reference (never < 65 mmHg)	16,230	247 (1.5%)	Ref = 1	
Q1 (1–5 min)	11,714	275 (2.3%)	1.01 (0.80–1.27)	0.93
Q2 (6–12 min)	9,442	270 (2.9%)	1.15 (0.90–1.45)	0.15
Q3 (13–28 min)	9,974	375 (3.8%)	1.34 (1.06–1.68)	0.0015†
Q4 (> 28 min)	9,955	593 (6.0%)	1.60 (1.28–2.01)	< 0.001†
Time > 20% decrease from baseline				0.046
Reference (never <20%)	6,112	123 (2.0%)	Ref = 1	
Q1 (1–16 min)	13,445	303 (2.3%)	0.82 (0.62–1.10)	0.10
Q2 (17–41 min)	12,502	310 (2.5%)	0.87 (0.64–1.17)	0.24
Q3 (42–90 min)	12,540	400 (3.2%)	0.96 (0.71–1.29)	0.72
Q4 (> 90 min)	12,716	624 (4.9%)	1.05 (0.76–1.45)	0.69
AUC for MAP under 65 mmHg				< 0.001
Reference(never < 65 mmHg)	16,230	247 (1.5%)	Ref = 1	
Q1 (1–16 mmHg · min)	10,355	216 (2.1%)	0.97 (0.76–1.25)	0.78
Q2 (17–41 mmHg · min)	10,251	292 (2.8%)	1.14 (0.90–1.44)	0.17
Q3 (42–90 mmHg · min)	10,239	379 (3.7%)	1.30 (1.04–1.63)	0.0035†
Q4 (> 91 mmHg · min)	10,240	626 (6.1%)	1.62 (1.30–2.02)	< 0.001†
AUC under % MAP decrease from baseline < 20%				< 0.001
Reference (never <20%)	6,112	123 (2.0%)	Ref = 1	
Q1 (1–83 % · min)	12,880	256 (2.0%)	0.78 (0.58–1.06)	0.042
Q2 (84–275 % · min)	12,733	328 (2.6%)	0.88 (0.66–1.19)	0.30
Q3 (276–728 % · min)	12,800	407 (3.2%)	0.97 (0.72–1.31)	0.79
Q4 (> 728 % · min)	12,790	646 (5.1%)	1.19 (0.87–1.64)	0.16
Time in the lowest MAP categories				< 0.001
Reference (never < 65 mmHg)	16,230	247 (1.5%)	Ref = 1	
60–65 mmHg			0.99 (0.78–1.28)	0.97
1 min	2,799	52 (1.9%)	0.95 (0.64–1.43)	0.77
2–4 min	3,859	81 (2.1%)	0.92 (0.66–1.30)	0.56
> 4 min	3,983	84 (2.1%)	1.11 (0.79–1.55)	0.44
55–60 mmHg			1.07 (0.85–1.35)	0.48
1 min	4,067	99 (2.4%)	1.06 (0.77–1.46)	0.64
2–4 min	4,393	131 (3.0%)	1.11 (0.83–1.50)	0.36
> 4 min	2,834	72 (2.5%)	1.01 (0.70–1.45)	0.94
50–55 mmHg			1.26 (0.99–1.59)	0.015
1 min	4,053	147 (3.6%)	1.35 (1.02–1.80)	0.008
2–4 min	3,308	138 (4.2%)	1.28 (0.96–1.72)	0.035
> 4 min	1,376	46 (3.3%)	0.98 (0.63–1.53)	0.91
< 50 mmHg			1.68 (1.35–2.08)	< 0.001†
1 min	3,607	173 (4.8%)	1.49 (1.13–1.96)	< 0.001
2–4 min	4,150	254 (6.1%)	1.63 (1.26–2.10)	< 0.001
> 4 min	2,656	236 (8.9%)	1.97 (1.50–2.59)	< 0.001
Time in the lowest % MAP decrease categories				< 0.001
Reference (never < 20%)	6,112	123 (2.0%)	Ref = 1	
20–30% decrease			0.70 (0.51–0.96)	0.0045†
1 min	1,354	36 (2.7%)	1.24 (0.74–2.08)	0. 30
2–4 min	2,418	43 (1.8%)	0.74 (0.46–1.19)	0.12
> 4 min	8,517	109 (1.3%)	0.61 (0.43–0.87)	< 0.001
30–40% decrease			0.87 (0.65–1.16)	0.22
1 min	3,226	68 (2.1%)	0.73 (0.49–1.10)	0.058
2–4 min	4,898	140 (2.9%)	0.93 (0.66–1.31)	0.61
> 4 min	9,935	251 (2.5%)	0.92 (0.67–1.25)	0.49
> 40% decrease			0.99 (0.74–1.34)	0.97
1 min	3,977	118 (3.0%)	0.89 (0.62–1.28)	0.44
2–4 min	4,816	200 (4.2%)	1.07 (0.77–1.49)	0.61
> 4 min	4,792	183 (3.8%)	1.09 (0.77–1.55)	0.52
> 50% decrease			1.46 (1.07–1.99)	0.0021†
1 min	2,644	145 (5.5%)	1.31 (0.92–1.88)	0.057
2–4 min	2,829	176 (6.2%)	1.34 (0.95–1.91)	0.036
> 4 min	1,797	168 (9.3%)	2.12 (1.45–3.09)	< 0.001

*Multivariable logistic model adjusting for covariates listed in table 1. Bonferroni correction was used to adjust for four comparisons within each exposure of interest. †$P < 0.05/4 = 0.0125$ was considered as statistically significant. For the detailed categories of minutes below absolute and relative thresholds (1, 2–4, greater than 4 min), the significance criterion was 0.05/12 = 0.0042.

AUC = area under curve; MAP = mean arterial pressure; MINS = myocardial injury after noncardiac surgery; OR = odds ratio.

Table 5. AKI: Multivariable Associations with Absolute and Relative MAP Thresholds

Threshold	Total (n = 57,315)	AKI (n = 3,870)	Adjusted OR (98.75% CI)*	*P* Values*
Time under MAP < 65 mmHg				< 0.001
Reference (never < 65 mmHg)	16,230	658 (4.1%)	Ref = 1	
Q1 (1–5 min)	11,714	570 (4.9%)	1.04 (0.89–1.22)	0.49
Q2 (6–12 min)	9,442	520 (5.5%)	1.15 (0.98–1.35)	0.032
Q3 (13–28 min)	9,974	597 (6.0%)	1.20 (1.02–1.40)	0.0049†
Q4 (> 28 min)	9,955	870 (8.7%)	1.35 (1.14–1.58)	< 0.001†
Time > 20% decrease from baseline				0.13
Reference (never <20%)	6,112	210 (3.4%)	Ref = 1	
Q1 (1–16 min)	13,445	612 (4.6%)	1.12 (0.90–1.38)	0.19
Q2 (17–41 min)	12,502	636 (5.1%)	1.15 (0.93–1.43)	0.10
Q3 (42–90 min)	12,540	729 (5.8%)	1.18 (0.95–1.47)	0.058
Q4 (> 90 min)	12,716	1,028 (8.1%)	1.27 (1.01–1.61)	0.010†
AUC under 65 mmHg				< 0.001
Reference(never < 65 mmHg)	16,230	658 (4.1%)	Ref = 1	
Q1 (1–16 mmHg * min)	10,355	517 (5.0%)	1.11 (0.95–1.30)	0.1051
Q2 (17–41 mmHg * min)	10,251	548 (5.3%)	1.12 (0.95–1.31)	0.086
Q3 (42–90 mmHg * min)	10,239	588 (5.7%)	1.13 (0.96–1.32)	0.064
Q4 (> 91 mmHg * min)	10,240	904 (8.8%)	1.34 (1.15–1.58)	< 0.001†
AUC under % MAP decrease from baseline < 20%				0.0021
Reference (never <20%)	6,112	210 (3.4%)	Ref = 1	
Q1 (1–83 % · min)	12,880	561 (4.4%)	1.10 (0.89–1.37)	0.26
Q2 (84–275 % · min)	12,733	676 (5.3%)	1.21 (0.97–1.50)	0.029
Q3 (276–728 % · min)	12,800	707 (5.5%)	1.12 (0.89–1.39)	0.21
Q4 (> 728 % · min)	12,790	1,061 (8.3%)	1.35 (1.07–1.70)	0.0013†
Time in the lowest MAP categories				< 0.001
Reference (never < 65 mmHg)	16,230	658 (4.1%)	Ref = 1	
60–65 mmHg			1.13 (0.96–1.32)	0.061
1 min	2,799	129 (4.6%)	1.05 (0.81–1.36)	0.62
2–4 min	3,859	209 (5.4%)	1.20 (0.97–1.49)	0.031
> 4 min	3,983	186 (4.7%)	1.11 (0.88–1.39)	0.26
55–60 mmHg			1.05 (0.90–1.23)	0.41
1 min	4,067	175 (4.3%)	0.89 (0.71–1.12)	0.23
2–4 min	4,393	243 (5.5%)	1.11 (0.90–1.36)	0.23
> 4 min	2,834	163 (5.8%)	1.22 (0.96–1.56)	0.039
50–55 mmHg			1.29 (1.10–1.51)	< 0.001†
1 min	4,053	254 (6.3%)	1.25 (1.02–1.54)	0.0061
2–4 min	3,308	237 (7.2%)	1.29 (1.04–1.61)	0.0029
> 4 min	1,376	108 (7.8%)	1.43 (1.06–1.92)	0.0031
< 50 mmHg			1.23 (1.05–1.44)	0.0010†
1 min	3,607	229 (6.3%)	1.10 (0.89–1.37)	0.26
2–4 min	4,150	315 (7.6%)	1.23 (1.00–1.50)	0.011
> 4 min	2,656	309 (11.6%)	1.43 (1.15–1.78)	< 0.0001
Time in the lowest % MAP decrease categories				0.022
Reference (never <20%)	6,112	210 (3.4%)	Ref = 1	
20–30% decrease			1.09 (0.88–1.36)	0.32
1 min	1,354	51 (3.8%)	1.02 (0.67–1.53)	0.93
2–4 min	2,418	101 (4.2%)	1.15 (0.83–1.58)	0.28
> 4 min	8,517	356 (4.2%)	1.09 (0.87–1.38)	0.33
30–40% decrease			1.14 (0.92–1.40)	0.12
1 min	3,226	145 (4.5%)	1.06 (0.79–1.41)	0.63
2–4 min	4,898	270 (5.5%)	1.23 (0.96–1.59)	0.036
> 4 min	9,935	519 (5.2%)	1.14 (0.91–1.43)	0.16
>40% decrease			1.24 (0.99–1.54)	0.015
1 min	3,977	236 (5.9%)	1.22 (0.94–1.59)	0.056
2–4 min	4,816	323 (6.7%)	1.20 (0.93–1.54)	0.078
> 4 min	4,792	363 (7.6%)	1.34 (1.04–1.73)	0.0042
> 50% decrease			1.35 (1.07–1.72)	0.0015†
1 min	2,644	200 (7.6%)	1.32 (0.99–1.76)	0.014
2–4 min	2,829	236 (8.3%)	1.26 (0.95–1.67)	0.043
> 4 min	1,797	205 (11.4%)	1.62 (1.19–2.20)	< 0.0001

*Multivariable logistic model adjusting for covariates listed in table 1. Bonferroni correction was used to adjust for four comparisons within each exposure of interest. †$P < 0.05/4 = 0.0125$ was considered as statistical significant. For the detailed categories of minutes below absolute and relative thresholds (1, 2–4, greater than 4 min), the significance criterion was 0.05/12 = 0.0042.

AKI = acute kidney injury; AUC = area under curve; MAP = mean arterial pressure, OR = odds ratio.

postoperative outcome was evaluated by Levin *et al.*[21] They found that hypertensive patients had more intraoperative blood pressure lability and that lability decreased mortality. In our study, however, there was no interaction between baseline pressure and the relationship between intraoperative hypotension and AKI. Intraoperative hypotension was thus proportionately related to AKI over the entire range of preoperative pressures.

In contrast, there was a significant interaction between baseline pressure and the relationship between intraoperative pressure and myocardial injury. However, the interaction was only substantive at intraoperative MAPs exceeding 65 mmHg. In the clinically relevant range of hypotensive pressures less than 65 mmHg, there was no important interaction. Preoperative blood pressure thus had no important effect on the relationship between intraoperative hypotension and myocardial injury.

From a clinical perspective, our interaction analysis thus indicates that anesthesiologists can manage intraoperative blood pressure without reference to preoperative values—a conclusion that differs starkly from classical anesthesia teaching that patients with high preoperative pressures should be maintained at relatively high pressures throughout surgery. A caveat, of course, is that we evaluated only two organs. It remains possible that preoperative pressures do matter for the brain and other physiologic functions such as gut permeability.

A novel aspect of our study is comparison between absolute and relative thresholds. Both were predictive. However, there was no advantage to using relative over absolute thresholds for AKI or myocardial injury. Absolute thresholds are easier to use since a reliable baseline pressure is not required. Furthermore, absolute thresholds are far easier to incorporate into decision support systems that would not normally have access to individual preoperative reference values. Therefore, we conclude that clinicians can use absolute thresholds to guide intraoperative blood pressure management.

We defined myocardial injury on the basis of increased cardiac enzymes. However, cardiac enzymes were not routinely measured even in relatively high-risk patients during the study period. Consequently, our analysis was mostly based on clinically apparent myocardial infarctions, thus underestimating the actual incidence of myocardial injury by about a factor-of-three.[1] Whether the relationships between hypotension and myocardial injury that we report apply comparably to silent injury remains unknown. However, the physiology is probably similar, suggesting that the relationships are probably similar.

As in any retrospective analysis, confounding and bias are concerns. For example, patients who experienced MINS or AKI were generally sicker and had more preoperative comorbidities. However, our large sample size and detailed registry allowed us to statistically adjust for many potential confounding factors. Our results are nonetheless surely somewhat degraded by both unknown and known but poorly characterized confounders. The extent to which either contributes is hard to assess.

About 60% of our patients had blood pressure measured oscillometrically at 1- to 5-min intervals. We linearly interpolated between measurements to provide reasonable estimates of intervening values, but is obviously less accurate than values from arterial catheters that were available at 1-min intervals. It seems unlikely that more frequent measurements would much change the harm thresholds we identified.

Conclusion

Pressures that until recently were considered clinically acceptable, for instance, a MAP of 65 mmHg, were associated with both myocardial and renal injuries. At lower pressures, the association was stronger and only brief exposures were required. Associations based on relative thresholds were no stronger than those based on absolute thresholds. Furthermore, there was no clinically important interaction with preoperative pressure. The extent to which the associations we observe are causal remains to be determined. But to the extent that they are, a strategy aimed at maintaining MAP above 65 mmHg appears to be as good as one based on the percentage reduction from baseline. This result is fortuitous because absolute thresholds are easier to use in that they do not require a reliable baseline pressure and can thus more easily be incorporated into decision support systems. While retrospective analyses cannot assess causality, our results suggest that maintaining intraoperative MAP greater than 65 mmHg may reduce the risk of AKI and myocardial injury—the leading cause of 30-day postoperative mortality.

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Competing Interests

The authors declare no competing interests.

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Appendix

Table A1. Summarized Statistics of MAP

Exposures	Mean ± SD	Median [Q1, Q3]	P10–P90
No. of baseline MAP reading	5 ± 3	4 [3, 6]	2–9
Baseline MAP	93 ± 10	93 [86, 99]	81–105
Preinduction MAP	101 ± 16	100 [90, 111]	82–122
TWA-MAP	84 ± 10	83 [77, 90]	72–97
Lowest MAP, mmHg, for cumulative minutes			
≥ 1	59 ± 11	59 [52, 66]	45–72
≥ 3	63 ± 10	63 [57, 69]	51–76
≥ 5	65 ± 9	64 [59, 70]	54–77
≥ 10	67 ± 9	67 [61, 73]	57–79
Lowest MAP, mmHg, for sustained minutes			
≥ 1	59 ± 11	59 [52, 66]	45–72
≥ 3	65 ± 9	64 [59, 70]	54–76
≥ 5	67 ± 9	67 [61, 72]	57–78
≥ 10	71 ± 9	71 [66, 77]	61–83
Lowest % MAP decrease from baseline (%) for cumulative minutes			
≥ 1	36 ± 13	36 [45, 28]	52–20
≥ 3	31 ± 12	32 [39, 24]	46–16
≥ 5	30 ± 12	30 [38, 22]	44–15
≥ 10	27 ± 11	27 [34, 20]	40–12
Lowest % MAP decrease from baseline for sustained minutes			
≥ 1	36 ± 13	36 [45, 28]	52–20
≥ 3	29 ± 12	30 [37, 22]	44–15
≥ 5	27 ± 11	27 [34, 20]	41–13
≥ 10	22 ± 11	23 [30, 15]	36–8
Minutes of MAP under absolute threshold, mmHg			
< 75	65 ± 76	41 [15, 87]	3–152
< 70	37 ± 53	19 [4, 47]	0–93
< 65	17 ± 32	6 [0, 20]	0–44
< 60	6 ± 16	1 [0, 6]	0–17
< 55	2 ± 7	0 [0, 2]	0–6
< 50	1 ± 3	0 [0, 0]	0–2
Minutes of % MAP decrease under relative threshold			
< 20	60 ± 76	33 [9,82]	0–150
< 30	20 ± 39	5 [0,21]	0–55
< 40	4 ± 13	0 [0,2]	0–10
< 50	1 ± 3	0 [0,0]	0–1
TWA of MAP, mmHg			
< 75	2.2 ± 2.5	1.3 [0.4, 3.1]	0–5.4
< 70	1.0 ± 1.5	0.5 [0.1, 1.3]	0–2.8
< 65	0.4 ± 0.8	0.1 [0.0, 0.5]	0–1.2
< 60	0.2 ± 0.4	0.0 [0.0, 0.1]	0–0.4
< 55	0.1 ± 0.2	0.0 [0.0, 0.0]	0–0.1
TWA of % MAP decrease from baseline, mmHg			
< 10	6.2 ± 5.6	4.6 [1.8, 9.2]	0.5–14.1
< 15	3.9 ± 4.3	2.4 [0.7, 5.8]	0.1–9.9
< 20	2.3 ± 3.1	1.1 [0.2, 3.1]	0–6.3
< 25	1.2 ± 2.0	0.4 [0.0, 1.5]	0–3.4
< 30	0.6 ± 1.2	0.1 [0.0, 0.6]	0–1.6
AUC of MAP, mmHg * min			
< 75	498 ± 722	262 [75, 630]	6–1,211
< 70	234 ± 414	94 [14, 276]	0–595
< 65	94 ± 211	22 [0, 101]	0–249
< 60	34 ± 98	1 [0, 28]	0–92
< 55	12 ± 44	0 [0, 4]	0–30
AUC of % MAP decrease from baseline, % * min			
< 10	1,421 ± 1,701	875 [323, 1,897]	76–3,265
< 15	904 ± 1,251	471 [137, 1,185]	15–2,198
< 20	526 ± 860	217 [41, 647]	0–1,340
< 25	275 ± 545	79 [6, 305]	0–720
< 30	129 ± 316	20 [0, 121]	0–335

AUC = area under curve; MAP = mean arterial pressure; TWA = time-weighted average.

Table A2. Multivariable Associations between Myocardial Injury after Noncardiac Surgery and Risk Factors

Factor	*df*	Chi-square	*P* Values
Cumulative minutes under Intraoperative MAP < 65 mmHg	4	43.55	< 0.0001
Surgical procedure	38	217.05	< 0.0001
Age, yr	1	142.96	< 0.0001
Congestive heart failure	1	93.81	< 0.0001
ASA status	1	83.18	< 0.0001
Emergency	1	76.94	< 0.0001
Weight loss	1	60.24	< 0.0001
Coagulopthy	1	57.73	< 0.0001
Fluid and electrolyte disorders	1	47.15	< 0.0001
Surgical time*	1	44.85	< 0.0001
Use of arterial catheter	1	36.84	< 0.0001
Peripheral vascular disease	1	20.37	< 0.0001
Chronic blood loss anemia	1	16.88	< 0.0001
Paralysis	1	15.86	< 0.0001
Intraoperative blood loss*	1	12.35	0.0004
Female	1	8.89	0.0029
Hypertension	1	8.56	0.0034
Other neurologic disorders	1	7.61	0.0058
Obesity	1	7.39	0.0066
ACE inhibitor	1	6.94	0.0084
Pulmonary circulation disease	1	6.92	0.0085
Baseline MAP	1	5.66	0.0173
Preoperative hemoglobin	1	3.65	0.0560
Chronic pulmonary disease	1	3.60	0.0579
Liver disease	1	2.96	0.0855
Race	2	2.58	0.2756
Renal failure	1	1.74	0.1875
Drug abuse	1	1.69	0.1932
Hypothyroidism	1	1.60	0.2062
Valvular disease	1	1.36	0.2432
Diuretic	1	0.90	0.3435
β-blocker	1	0.59	0.4430
Deficiency anemias	1	0.51	0.4765
Psychoses	1	0.41	0.5209
Calcium channel blocker	1	0.39	0.5331
Baseline EGFR*	1	0.38	0.5369
Lymphoma	1	0.28	0.5991
Rheumatoid arthritis/collagen vas	1	0.23	0.6330
Alcohol abuse	1	0.21	0.6496
Depression	1	0.14	0.7042
Tumor	1	0.07	0.7935
Metastatic cancer	1	0.06	0.7989
Angiotensin receptor blockers	1	0.05	0.8174
Diabetes	1	0.00	0.9637

*Logarithmic-transformed in the multivariable logistic model.

ACE = angiotensin-converting enzyme; ASA = American Society of Anesthesiologists; *df* = degrees of freedom; EGFR = estimated glomerular filtration rate; MAP = mean arterial pressure.

Table A3. Multivariable Associations between Acute Kidney Injury and Risk Factors

Factor	*df*	Chi-square	*P* Values
Cumulative minutes under Intraoperative MAP < 65 mmHg	4	24.89	< 0.0001
Surgical procedure	44	945.63	< 0.0001
Female	1	171.09	< 0.0001
Weight loss	1	151.85	< 0.0001
Preoperative hemoglobin	1	94.91	< 0.0001
Baseline MAP	1	86.51	< 0.0001
Coagulopthy	1	61.94	< 0.0001
ASA status	1	50.72	< 0.0001
Obesity	1	44.74	< 0.0001
Surgical time*	1	44.66	< 0.0001
Intraoperative blood loss*	1	43.04	< 0.0001
Congestive heart failure	1	41.59	< 0.0001
Fluid and electrolyte disorders	1	29.65	< 0.0001
Renal failure	1	27.19	< 0.0001
Race	2	21.06	< 0.0001
Diabetes	1	20.24	< 0.0001
Emergency	1	18.21	< 0.0001
Age, yr	1	10.79	0.0010
Angiotensin receptor blockers	1	9.72	0.0018
Hypertension	1	7.22	0.0072
Calcium channel blocker	1	6.41	0.011
Chronic pulmonary disease	1	3.19	0.074
Alcohol abuse	1	3.07	0.080
β-blocker	1	2.76	0.097
Diuretic	1	2.21	0.14
Hypothyroidism	1	2.21	0.14
Rheumatoid arthritis/collagen vas	1	2.20	0.14
Liver disease	1	1.94	0.16
Peripheral vascular disease	1	1.89	0.17
Use of arterial catheter	1	1.84	0.17
Chronic blood loss anemia	1	1.64	0.20
Valvular disease	1	1.09	0.30
Metastatic cancer	1	0.80	0.37
Baseline EGFR*	1	0.73	0.39
Lymphoma	1	0.57	0.45
Tumor	1	0.48	0.49
ACE inhibitor	1	0.43	0.51
Deficiency anemias	1	0.06	0.80
Paralysis	1	0.03	0.86
Pulmonary circulation disease	1	0.02	0.89
Psychoses	1	0.02	0.89
Depression	1	0.02	0.89
Other neurologic disorders	1	0.01	0.93
Drug abuse	1	0.00	0.96

*Logarithmic-transformed in the multivariable logistic model.

ACE = angiotensin-converting enzyme; ASA = American Society of Anesthesiologists; EGFR = estimated glomerular filtration rate; MAP = mean arterial pressure.