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Intraoperative Hypotension and Acute Kidney Injury after Noncardiac Surgery in Infants and Children: A Retrospective Cohort Analysis

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Intraoperative hypotension is associated with acute kidney injury in adults having noncardiac surgery
- In children, there are no data defining the association between hypotension and kidney injury

What This Article Tells Us That Is New

- In a large cohort of pediatric surgical patients in whom creatinine concentrations were measured preoperatively and postoperatively, there was no association between lowest mean arterial pressure and acute kidney injury
- There was also no association between largest percentage reduction in mean arterial pressure and acute kidney injury

ABSTRACT

Background: Age- and sex-specific reference nomograms for intraoperative blood pressure have been published, but they do not identify harm thresholds. The authors therefore assessed the relationship between various absolute and relative characterizations of hypotension and acute kidney injury in children having noncardiac surgery.

Methods: The authors conducted a retrospective cohort study using electronic data from two tertiary care centers. They included inpatients 18 yr or younger who had noncardiac surgery with general anesthesia. Postoperative renal injury was defined using the Kidney Disease Improving Global Outcomes definitions, based on serum creatinine concentrations. The authors evaluated potential renal harm thresholds for absolute lowest intraoperative mean arterial pressure (MAP) or largest MAP reduction from baseline maintained for a cumulative period of 5 min. Separate analyses were performed in children aged 2 yr or younger, 2 to 6 yr, 6 to 12 yr, and 12 to 18 yr.

Results: Among 64,412 children who had noncardiac surgery, 4,506 had creatinine assessed preoperatively and postoperatively. The incidence of acute kidney injury in this population was 11% (499 of 4,506): 17% in children under 6 yr old, 11% in children 6 to 12 yr old, and 6% in adolescents, which is similar to the incidence reported in adults. There was no association between lowest cumulative MAP sustained for 5 min and postoperative kidney injury. Similarly, there was no association between largest cumulative percentage MAP reduction and postoperative kidney injury. The adjusted estimated odds for kidney injury was 0.99 (95% CI, 0.94 to 1.05) for each 5-mmHg decrease in lowest MAP and 1.00 (95% CI, 0.97 to 1.03) for each 5% decrease in largest MAP reduction from baseline.

Conclusions: In distinct contrast to adults, the authors did not find any association between intraoperative hypotension and postoperative renal injury. Avoiding short periods of hypotension should not be the clinician's primary concern when trying to prevent intraoperative renal injury in pediatric patients.

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Intraoperative hypotension is common in infants, with the incidence varying widely depending on patient age and how hypotension is defined.[1] Age- and sex-specific reference nomograms for intraoperative blood pressure have been published,[2] but they do not identify harm thresholds. Nor is it clear whether intraoperative pediatric hypotension should be defined by absolute thresholds or relative to individual baseline blood pressure.[3]

In a survey study, for example, most pediatric anesthesiologists defined intraoperative hypotension as a 20 to 30% relative reduction in baseline systolic blood pressure.[4] However, there are no data to support this threshold, and perhaps consequently, there is no consensus definition for intraoperative hypotension for pediatric patients.

Hypotension during noncardiac surgery is linked to end-organ damage in adults, with distinct absolute and relative mean arterial pressure (MAP) thresholds under which

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the risk of acute kidney injury (AKI) and myocardial injury increase.[5–8] Although AKI is common after cardiac surgery in children,[9–12] little is known about the relationship between intraoperative blood pressure and AKI for pediatric noncardiac surgery.[13,14]

We therefore tested the hypothesis that children with intraoperative hypotension are likely to develop postoperative AKI, and aimed to assess the relationship between various absolute and relative characterizations of hypotension and AKI in children having noncardiac surgery. As in previous adult studies,[6] absolute hypotension was defined as lowest intraoperative MAP sustained for 5 cumulative minutes. Relative hypotension was determined by the maximum percentage reduction in MAP from preoperative baseline, again sustained for 5 cumulative minutes. Our primary goal was to estimate the relationship between lowest cumulative intraoperative pressures and postoperative AKI in children of various ages, and to assess apparent harm thresholds.

Materials and Methods

With Cleveland Clinic (Cleveland, Ohio) and University of Texas Southwestern Medical Center (Dallas, Texas) Institutional Review Board approvals and waived consent, we conducted a retrospective cohort study using electronic data from the Cleveland Clinic Perioperative Health Documentation System and Children's Health Medical Center at Dallas, Texas Epic (USA) electronic medical records. We included inpatients less than 18 yr of age who had noncardiac surgery with general anesthesia between 2010 through 2017. We also required gestational age greater than 37 weeks at birth if available, surgical duration greater than 60 min, preoperative and at least one postoperative serum creatinine measurement within 7 days of surgery, and at least one preoperative baseline blood pressure. Baseline blood pressure was taken from a preoperative visit when available, or from the preoperative area on the day of surgery.

We defined preexisting medical conditions using International Classification of Diseases, Ninth Revision or Tenth Revision, billing codes, and included only those fulfilling at least one of the following: (1) appeared in the patient "problem list" with the date preceding the date of surgery; (2) appeared on International Classification of Diseases, Ninth Revision or Tenth Revision, lists before the index surgery; or (3) were flagged as a chronic International Classification of Diseases, Ninth Revision or Tenth Revision, condition based on Healthcare Cost and Utilization Project definitions using diagnosis codes referenced to Elixhauser Comorbidity software (https://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comorbidity.jsp).

We excluded patients who had (1) known chronic kidney disease, defined as preoperative estimated glomerular filtration rate of less than 60 ml · min^{-1} · 1.73 m^{-2} or requiring dialysis; (2) having urological procedures or renal transplantation; (3) preoperative intensive care unit admission; (4) previous surgery during current admission; (5) preoperative total parenteral nutrition; (6) fewer than six blood pressures recorded per hour of surgery; and (7) missing potential confounding factors needed for the primary analysis (Supplemental Digital Content table 1, http://links.lww.com/ALN/C744).

Postoperative AKI was defined using the Kidney Disease Improving Global Outcomes definitions based on serum creatinine concentrations (Supplemental Digital Content table 2, http://links.lww.com/ALN/C745). We used the most proximal preoperative creatinine concentration as the baseline and the highest recorded postoperative creatinine concentration within 7 days of surgery as the postoperative concentration. According to the Kidney Disease Improving Global Outcomes definition, patients were considered to have AKI if the postoperative value was more than 1.5 times baseline or increased more than 0.3 mg/dl in any 48-hour period. Our primary outcome was a binary variable defined as having AKI (stage 1 to 3) *versus* no kidney injury. We divided the children into the following five categories based on age: 28 days or younger, 29 days to 2 yr, 2 to 6 yr, 6 to 12 yr, and 12 to 18 yr.

Intraoperative MAPs were recorded electronically in each medical center's documentation system. When blood pressure was measured noninvasively, it was generally recorded at 2- to 5-min intervals. When an arterial catheter was used, MAP was available every minute. An artifact removal algorithm was used to clean the raw blood pressure monitoring data based on the range and abrupt change (details in Supplemental Digital Content table 3, http://links.lww.com/ALN/C746). Blood pressure measurements with a gap smaller than 10 min were linearly interpolated to construct minute-by-minute data.

We determined the relationship between the absolute minimum intraoperative MAP measured for at least 5 cumulative minutes (lowest MAP) and the largest intraoperative MAP percent reduction from baseline for at least 5 cumulative minutes (largest MAP reduction from baseline) and AKI in an effort to identify AKI harm thresholds.

Statistical Methods

The statistical analysis plan was developed *a priori* and included in our original Institutional Review Board applications.

For the primary outcome (AKI stage 1 to 3 *versus* stage 0), we explored potential AKI thresholds for absolute lowest MAP or largest MAP reduction from baseline for 5 cumulative minutes. Because there were so few AKI events in children 28 days old and younger, all patients 2 yr old and younger were aggregated. We used univariate smoothed moving-average plots for each of the remaining four age groups: children aged 2 yr or younger, 2 to 6 yr, 6 to 12 yr, and 12 to 18 yr. The univariate smoothed moving-average plot iteratively calculated the crude AKI probability at each smoothed exposure point by using k points (window size) that were nearest to the smoothed exposure point. The step

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from last smoothed point to the next one was determined by moving size. We used 10% of the corresponding group sample size as the window size and 1% of corresponding sample size as moving size.

For each absolute lowest MAP or relative largest MAP reduction, we fitted a multivariable logistic regression model with restricted cubic spline function having three knots located at the 10th, 50th, and 90th exposure percentiles, adjusting for potential confounders. An interaction between age group and spline terms was also added to the model to see if the relationship shape between exposure and AKI at each age group differed (interaction term $P < 0.15$). If no interaction was found, we would assess the spline terms of exposure across all age groups. If we did not find a nonlinear relationship between exposure and AKI, we would fit a logistic regression model adjusting for confounders, with interactions between age group and corresponding exposure. We would report the association between exposure and AKI separately for each age group if the age-by-exposure interaction was significant ($P < 0.15$). Otherwise, we would report one adjusted odds ratio for 5-mmHg changes in lowest MAP or 5% change in largest MAP decrease.

In a secondary analysis, we considered degrees of renal injury separately as no AKI, stage 1, and stage 2/3 (aggregated due to small numbers of events) and explored relationships between both exposures and outcomes, adjusting for confounders.

Summary statistics are presented as means ± SDs, medians [quartile 1, quartile 3], or N (%) as appropriate and corresponding univariate odds ratio of AKI associated with unit change (continuous variable) or having this exposure (binary variable) was also reported. The *P* value of univariate association between summary variables and AKI was obtained from ANOVA, Kruskal–Wallis test, Pearson's chi-square test, or Fisher exact test as appropriate. All potential confounders were adjusted for in each multivariable analysis including demographic and morphometric characteristics, preoperative comorbidities, preoperative laboratory values, and preoperative medication use, along with American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status, type and length of surgery, and intraoperative variables (see detail in table 1). We adjusted for baseline blood pressure when considering absolute thresholds, but not for relative thresholds, because baseline MAP was incorporated into the definition of relative reduction.

Post Hoc Analyses

We also conducted two *post hoc* analyses. The first ignored interactions with age group. For each exposure, a logistic regression model was fitted with splines of lowest MAP or largest MAP reduction from baseline at the 10th, 50th, and 90th percentiles ignoring any interaction between corresponding exposure spline term and age group. Specifically, we considered age to be a continuous confounder, along with the other confounders used in primary analysis, to determine whether there was an overall exposure threshold.

The second *post hoc* analysis considered a study site–exposure interaction. For each exposure, a logistic regression model was fitted with spline terms of exposure at the 10th, 50th, and 90th percentiles and an interaction term for study site and exposure (lowest MAP or largest MAP reduction from baseline) to assess whether exposure thresholds differed between the two study sites.

We conducted one sensitivity analysis additionally adjusting for intraoperative blood loss. However, that analysis was restricted to Cleveland Clinic data since this variable was missing in more than 800 cases from the Dallas site.

All hypothesis testing was equal two-tailed with a significance level of 0.15 for interaction and 0.05 for marginal relationship in both primary and secondary analyses. All the analyses were conducted in SAS studio 3.7 Basic Edition (2012 to 2017; SAS Institute Inc., USA).

Sample Size Considerations

A priori, we expected to have between 50,000 and 150,000 patients meeting study inclusion/exclusion criteria. With at least 50,000 patients and incidence of stage 1 AKI of 2% or more, we would have a statistical power of 90% or more to detect an odds ratio of AKI greater than 1.05 associated with each 5-mmHg decrease in lowest MAP, assuming that the lowest MAP has a normal distribution with a mean of 60 mmHg and a SD of 12 mmHg. A third site originally expected to participate in the study was not included due to data collection difficulty, resulting in fewer eligible patients.

We also performed a *post hoc* analysis to assess the effect size we could detect based on actual data. The lowest MAP had a normal distribution with a mean of 60 mmHg and a SD of 12 mmHg, and the incidence of AKI was estimated to be 11%. With our current sample size, we had a power of 0.9 or more to detect an odds ratio of AKI greater than 1.08 associated with each 5-mmHg decrease in lowest MAP with a type I error of 0.05. Our achieved precision resulted in a narrow CI, ranging from 0.94 to 1.05.

Results

Among 64,412 pediatric patients who had noncardiac surgery between 2010 and 2017, 5,618 patients met our inclusion and exclusion criteria (fig. 1). We further excluded 1,112 patients who were missing intraoperative blood pressure data, were missing confounding variables, or had fewer intraoperative BP recordings than required. Finally, a total of 4,506 cases were included in our final analysis, 2,324 cases from the Cleveland Clinic and 2,182 from Children's Health. Baseline, preoperative, intraoperative, and postoperative characteristics are summarized for patients who did and did not develop AKI in table 1. Characteristics were also summarized by tertiles of lowest intraoperative MAP for a cumulative of 5 min (Supplemental Digital Content

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Table 1. Baseline, Intraoperative and Postoperative Characteristics by AKI (N = 4,506)

Factor	Total (N = 4,506)	No AKI (N = 4,007)	AKI (N = 499)	Odds Ratio (95% CI)§	*P* Value
Age, yr	9.6 ± 5.8	9.9 ± 5.8	7.0 ± 5.5	0.92 (0.90–0.93)	< 0.001‖
Age group†					< 0.001**
< 2 yr	706 (16)	582 (15)	124 (25)	Reference	
2–6 yr	778 (17)	644 (16)	134 (27)	0.98 (0.75–1.28)	
6–12 yr	1,062 (24)	940 (24)	122 (24)	0.61 (0.46–0.80)	
12–18 yr	1,960 (43)	1,841 (46)	119 (24)	0.30 (0.23–0.40)	
Lowest intraoperative MAP sustained for at least a cumulative 5 min, mmHg	60 [53, 67]	60 [53, 67]	60 [53, 66]	1.00 (0.99–1.01)	0.690#
Female (%)†	2,080 (46)	1,849 (46)	231 (46)	1.01 (0.83–1.21)	0.960**
Weight, kg†	38 ± 26	39 ± 27	28 ± 22	0.98 (0.98–0.98)	< 0.001‖
Baseline MAP, mmHg†	79 ± 12	79 ± 12	80 ± 13	1.00 (1.00–1.01)	0.240‖
< 2 yr	71 ± 16	70 ± 15	74 ± 16	1.02 (1.01–1.03)	0.006‖
2–6 yr	78 ± 12	78 ± 12	81 ± 12	1.02 (1.00–1.03)	0.010‖
6–12 yr	79 ± 11	79 ± 11	81 ± 10	1.02 (1.00–1.03)	0.100‖
12–18 yr	83 ± 9	83 ± 9	84 ± 10	1.02 (1.00–1.04)	0.100‖
ASA Physical Status					< 0.001**
I–II	1,769 (39)	1,674 (42)	95 (19)	Reference	
III	2,396 (53)	2,078 (52)	318 (64)	2.70 (2.13–3.42)	
IV–V	341 (8)	255 (6)	86 (17)	5.94 (4.32–8.19)	
Race†					< 0.001**
Black	604 (13)	522 (13)	82 (16)	Reference	
Other	742 (17)	639 (16)	103 (21)	1.03 (0.75–1.40)	
White	3,160 (70)	2,846 (71)	314 (63)	0.70 (0.54–0.91)	
Preoperative variables					
Preoperative creatinine, mg/dl†	0.50 [0.31, 0.67]	0.50 [0.36, 0.70]	0.30 [0.20, 0.49]	0.65 (0.62–0.69)	< 0.001#
Preoperative hemoglobin, g/dl†	12.0 [10.3, 13.4]	12.1 [10.5, 13.5]	10.6 [9.2, 12.0]	0.77 (0.74–0.81)	< 0.001#
Preoperative sepsis†	268 (6)	223 (6)	45 (9)	1.68 (1.20–2.35)	0.002**
History of organ transplant†	177 (4)	140 (4)	37 (7)	2.21 (1.52–3.22)	< 0.001**
Preoperative tacrolimus use†	114 (3)	93 (2)	21 (4)	1.85 (1.14–3.00)	0.011**
Preoperative cyclosporine use†	17 (0.4)	13 (0.3)	4 (0.8)	2.48 (0.81–7.64)	0.110††
Preoperative furosemide use†	255 (6)	193 (5)	62 (12)	2.80 (2.07–3.80)	< 0.001**
Preoperative comorbidity					
Congestive heart failure	27 (0.6)	18 (0.5)	9 (2)	4.07 (1.82–9.11)	< 0.001**
Valvular disease	64 (1.4)	51 (1.3)	13 (2.6)	2.07 (1.12–3.84)	0.018**
Pulmonary circulation disease	28 (0.6)	28 (0.7)	0 (0.0)	—	0.066††
Peripheral vascular disease	43 (1)	37 (0.9)	6 (1.2)	1.31 (0.55–3.11)	0.550**
Hypertension†	282 (6.3)	228 (5.7)	54 (11)	2.01 (1.47–2.75)	< 0.001**
Paralysis	405 (9.0)	370 (9.2)	35 (7.0)	0.74 (0.52–1.06)	0.100**
Other neurologic disorders	717 (16)	664 (17)	53 (11)	0.60 (0.44–0.80)	< 0.001**
Chronic pulmonary disease†	358 (7.9)	321 (8.0)	37 (7.4)	0.92 (0.65–1.31)	0.640**
Diabetes without chronic complications	53 (1.2)	41 (1.0)	12 (2.4)	2.38 (1.24–4.57)	0.007**
Hypothyroidism	91 (2.0)	76 (1.9)	15 (3.0)	1.60 (0.91–2.81)	0.097**
Liver disease†	220 (4.9)	155 (3.9)	65 (13)	3.72 (2.74–5.06)	< 0.001**
Chronic peptic ulcer disease	15 (0.3)	14 (0.4)	1 (0.2)	0.57 (0.08–4.36)	1.000††
Lymphoma	110 (2.4)	101 (2.5)	9 (1.8)	0.71 (0.36–1.41)	0.330**
Metastatic cancer	157 (3.5)	124 (3.1)	33 (6.6)	2.22 (1.49–3.29)	< 0.001**
Solid tumor without metastasis	299 (6.6)	264 (6.6)	35 (7.0)	1.07 (0.74–1.54)	0.720**
Rheumatoid arthritis/collagen vascular disease	28 (0.6)	25 (0.6)	3 (0.6)	0.96 (0.29–3.20)	1.000††
Coagulopathy	308 (6.8)	223 (5.6)	85 (17)	3.49 (2.66–4.56)	< 0.001**
Obesity†	203 (4.5)	171 (4.3)	32 (6.4)	1.54 (1.04–2.27)	0.029**
Weight loss†	499 (11)	391 (9.8)	108 (22)	2.55 (2.02–3.24)	< 0.001**
Fluid and electrolyte disorders†	941 (21)	793 (20)	148 (30)	1.71 (1.39–2.10)	< 0.001**
Chronic blood loss anemia†	106 (2.4)	89 (2.2)	17 (3.4)	1.55 (0.92–2.63)	0.099**
Deficiency anemias†	667 (15)	559 (14)	108 (22)	1.70 (1.35–2.15)	< 0.001**

(*Continued*)

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Table 1. (Continued)

Factor	Total (N = 4,506)	No AKI (N = 4,007)	AKI (N = 499)	Odds Ratio (95% CI)§	*P* Value
Intraoperative variables†					
Norepinephrine, mg	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	1.00 (1.00–1.00)	< 0.001#
Phenylephrine, mg	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	1.00 (1.00–1.00)	< 0.001#
Ephedrine, mg	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.76 (0.61–0.96)	0.001#
Vasopressor use	672 (15)	636 (16)	36 (7.2)	0.41 (0.29–0.58)	< 0.001**
Norepinephrine	36 (0.8)	21 (0.5)	15 (3.0)	5.88 (3.01–11.49)	< 0.001**
Phenylephrine	613 (14)	588 (15)	25 (5.0)	0.31 (0.20–0.46)	< 0.001**
Ephedrine	117 (2.6)	115 (2.9)	2 (0.40)	0.14 (0.03–0.55)	0.0002††
Crystalloid, ml	675.0 [300.0, 1500.0]	700.0 [300.0, 1600.0]	375.0 [200.0, 850.0]	1.00 (1.00–1.00)	< 0.001#
Blood loss*	20.0 [5.0, 100.0]	20.0 [5.0, 100.0]	10.0 [3.0, 100.0]	1.00 (1.00–1.00)	0.260#
Use of intravenous contrast material	189 (4.2)	151 (3.8)	38 (7.6)	2.11 (1.46–3.04)	< 0.001**
Ketorolac	485 (11)	463 (12)	22 (4.4)	0.35 (0.23–0.55)	< 0.001**
Gentamycin	88 (2.0)	78 (1.9)	10 (2.0)	1.03 (0.53–2.00)	0.930**
Vancomycin	285 (6.3)	254 (6.3)	31 (6.2)	0.98 (0.67–1.44)	0.910**
Emergent surgery†	691 (15)	607 (15)	84 (17)	1.13 (0.88–1.46)	0.320**
Surgery type†					< 0.001**
Miscellaneous diagnostic and therapeutic procedures	340 (7)	256 (6)	84 (17)	Reference	
Operations on the cardiovascular system‡	250 (5)	226 (6)	24 (5)	0.32 (0.20–0.53)	
Operations on the digestive system	1,560 (35)	1,402 (35)	158 (31)	0.34 (0.26–0.46)	
Operations on the hemic and lymphatic system	254 (6)	191 (5)	63 (13)	1.01 (0.69–1.47)	
Operations on the integumentary system	244 (5)	212 (5)	32 (6)	0.46 (0.29–0.72)	
Operations on the musculoskeletal system	568 (13)	535 (13)	33 (7)	0.19 (0.12–0.29)	
Operations on the nervous system	853 (19)	805 (20)	48 (10)	0.18 (0.12–0.27)	
Operations on the respiratory system	169 (4)	140 (4)	29 (6)	0.63 (0.40–1.01)	
Operations on the urinary system	86 (2)	76 (2)	10 (2)	0.40 (0.20–0.81)	
Others	182 (4)	164 (4)	18 (3)	0.33 (0.19–0.58)	
Surgery duration, min†	217 ± 156	216 ± 151	224 ± 193	1.00 (1.00–1.01)	0.280‖
Intraoperative time-weighted average MAP, mmHg	70 ± 11	70 ± 11	70 ± 11	1.00 (0.99–1.01)	0.820‖
Intraoperative mean MAP, mmHg	70 ± 11	70 ± 11	70 ± 11	1.00 (0.99–1.01)	0.830‖
Intraoperative blood pressure measurement, arterial catheter†	1,224 (27)	1,096 (27)	128 (26)	0.92 (0.74–1.13)	0.420**

Summary statistics are presented as mean ± SD, median [25th, 75th percentile], or N (%). Surgery type was grouped by the Agency for Healthcare Research and Quality (Rockville, Maryland) Clinical Classifications Software for Services and Procedures, and low-frequency event or nonevent categories (N < 10) were grouped into the "Other" group.

*Data not available for all subjects. Missing values: intraoperative blood loss = 654. †Confounders adjusted for in the multivariable analysis. Baseline blood pressure was only adjusted for when the exposure was lowest MAP and site was also adjusted for in all the multivariable analyses. ‡Operations on cardiovascular system included other vascular catheterization; not heart, peripheral vascular bypass, other vascular bypass and shunt; not heart, hemodialysis, other operating room procedures on vessels of head and neck, embolectomy and endarterectomy of lower limbs, other operating room procedures on vessels other than head and neck, other diagnostic cardiovascular procedures, and other non–operating room therapeutic cardiovascular procedures. §Univariate odds ratio associated with each unit increase of risk factors (if continuous) or having the corresponding factor (if binary) was reported. The change scale for preoperative creatinine was 0.01 mg/dl increase and for surgery duration was every 10-min increase. *P* values: ||ANOVA, #Kruskal–Wallis test, **Pearson's chi-square test, and ††Fisher exact test.

AKI, acute kidney injury; ASA, American Society of Anesthesiologists; MAP, mean arterial pressure.

table 4, http://links.lww.com/ALN/C747) and by site (Supplemental Digital Content table 5, http://links.lww.com/ALN/C748). About 43% (1,960 of 4,506) of the sample was in the 12- to 18-yr-old age group. The overall mean ± SD age was 10 ± 6 yr, and mean ± SD baseline MAP was 79 ± 12 mmHg. About 60% (2,737 of 4,506) of patients were designated ASA Physical Status III or greater.

Of the patients, 33% (1,487 of 4,506) had creatinine measured on each of the first 3 postoperative days. The median [quartile 1, quartile 3] of intraoperative lowest MAP maintained for at least a cumulative 5 min was 60 [53, 67] mmHg, and the median [quartile 1, quartile 3] of the largest MAP reduction from baseline was –25% [–33%, –15%]. Time-weighted average MAP (calculated as area under the MAP curve divided by total measurement time) by age and site is shown in Supplemental Digital Content table 6 (http://links.lww.com/ALN/C749). The overall incidence of postoperative AKI was 499 of 4,506 (11%) in the study population (104 cases from Cleveland Clinic and 395 from Children's Health). Among these, 342 of 4,506 (7.6%) patients had stage 1 AKI, 117 of 4,506 (2.6%) had stage 2 AKI, and 40 of 4,506 (0.9%) had stage 3 AKI. AKI incidences by age and site are shown in Supplemental Digital Content table 7 (http://links.lww.com/ALN/C750).

Figure 2 shows the unadjusted moving average plots for the raw association between postoperative AKI and lowest MAP for at least 5 cumulative minutes. We did not see evidence of a clear threshold between lowest MAP and postoperative AKI. Figure 3 shows the unadjusted smooth moving average plot for the association between postoperative AKI and largest percentage MAP reduction from

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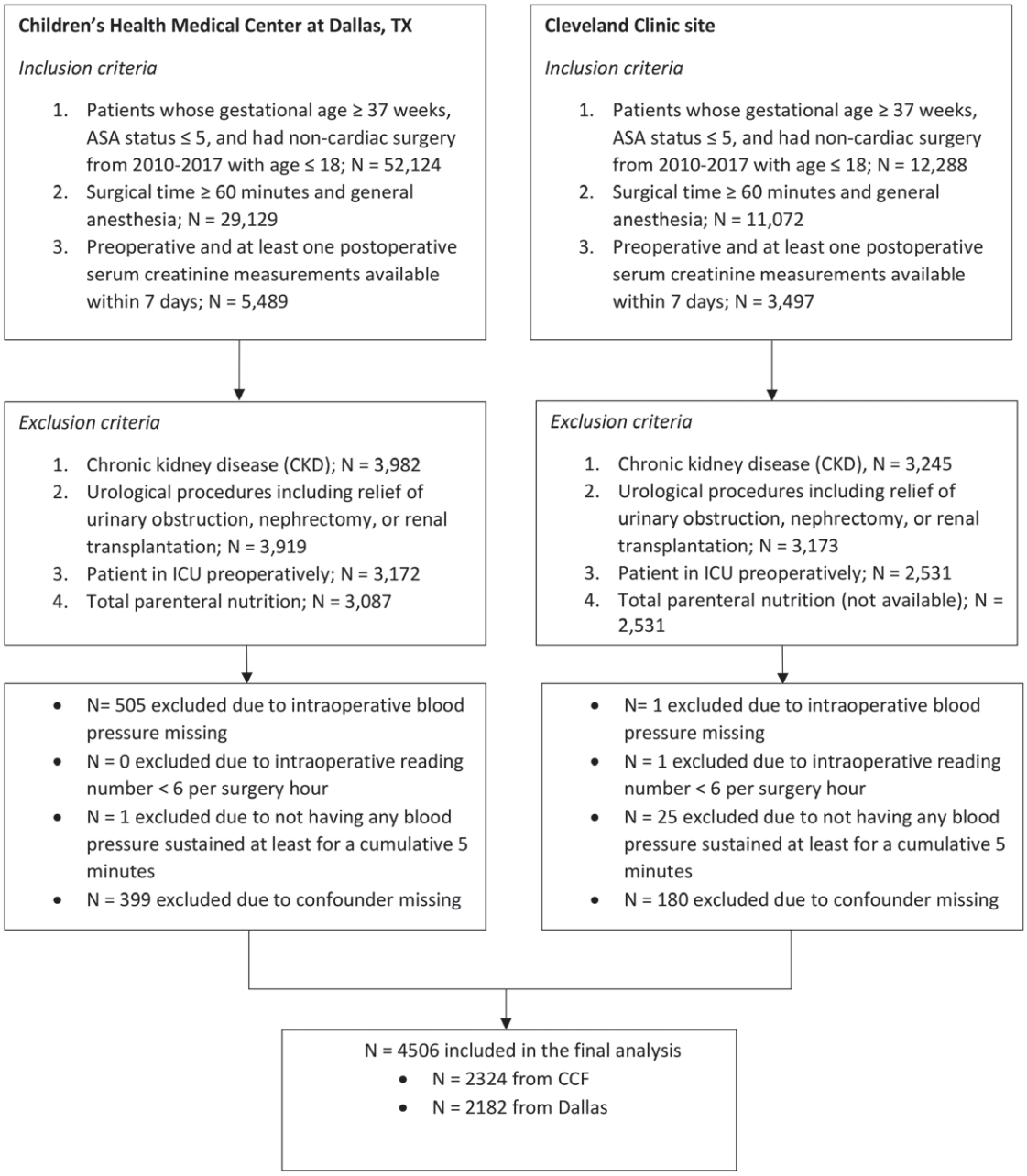

Fig. 1. Study population flowchart. ASA, American Society of Anesthesiologists; ICU, intensive care unit.

baseline. Similarly, we did not see a clear threshold between largest percentage MAP reduction and postoperative AKI.

The multivariable spline smoothing plot for lowest cumulative MAP and largest MAP reduction from baseline and postoperative AKI by age group are shown in figure 4. The relationship shape across age groups was similar, with nonsignificant interactions between splines of lowest MAP and age group ($P = 0.779$) and largest percentage MAP reduction from baseline and age group ($P = 0.980$) from the multivariable logistic regression model with spline in terms of exposure at the 10th, 50th, and 90th percentiles. The spline terms of lowest MAP and largest MAP reduction from baseline were also not significant ($P = 0.960$ and $P = 0.190$) in a "main effects" model without the interaction term, indicating absence of a nonlinear relationship between either the lowest MAP or largest percentage MAP reduction from baseline documented for at least a cumulative 5 min and postoperative AKI.

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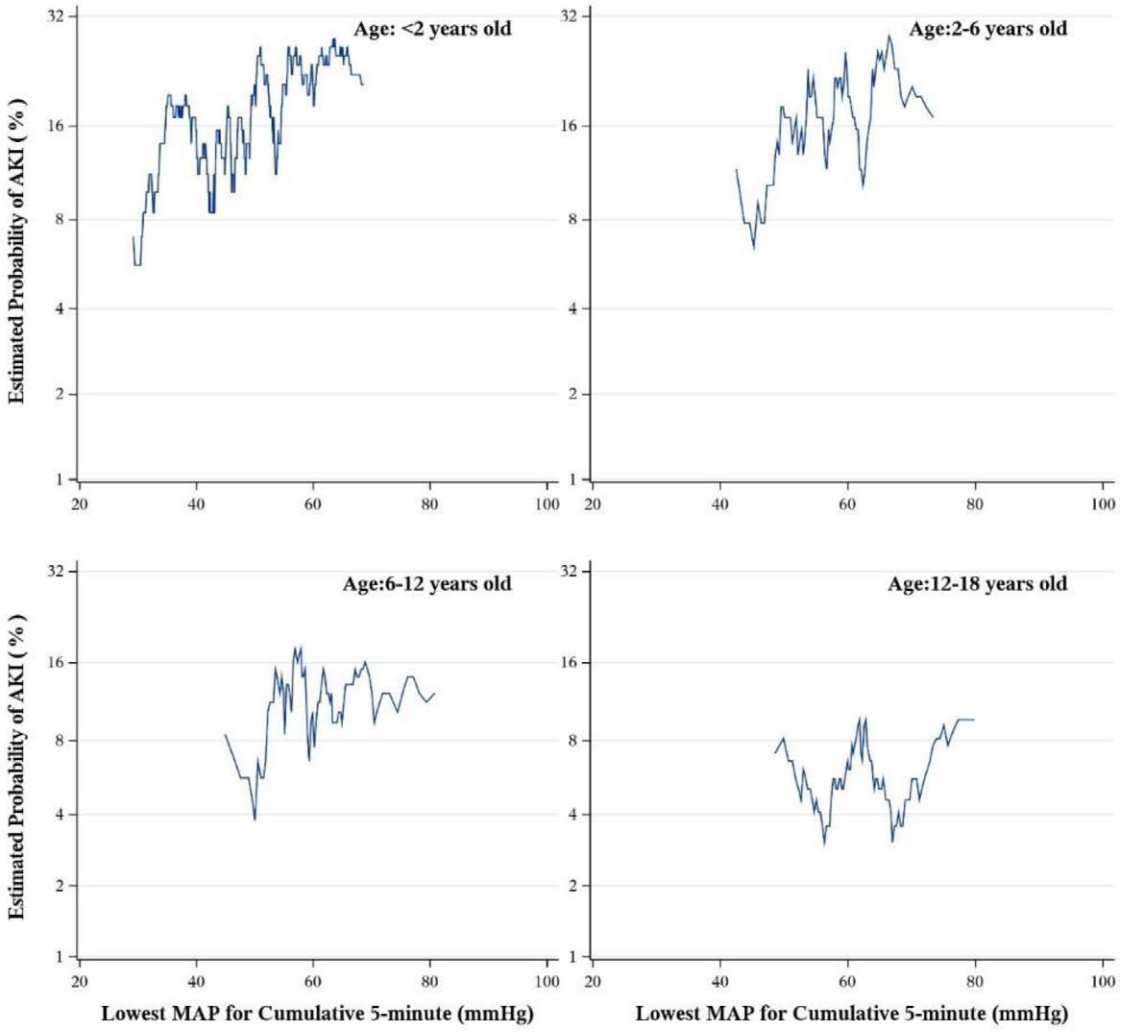

Fig. 2. Smooth moving average plot of risk of acute kidney injury (AKI) and lowest mean arterial pressure (MAP) for at least a cumulative 5 min—all patients.

Since we were unable to find absolute or relative MAP thresholds associated with AKI, we then explored the linear relationship between MAP and AKI. We did not find evidence of association between either the lowest MAP or largest percentage MAP reduction from baseline and postoperative AKI in univariate or multivariable regression models. Estimated odds ratios with 95% CIs of these exposures and outcome are shown in table 2.

The secondary analysis treating AKI separately as no AKI, stage 1, and stage 2/3 did not identify a relationship between lowest MAP and AKI stages with an estimated adjusted proportional odds ratio of 1.00 (95% CI, 0.95 to 1.06) associated with each 5-mmHg decrease in the lowest MAP maintained for at least 5 min. The relationship between largest MAP reduction from baseline and AKI stages was also not significant with an estimated proportional odds ratio of 0.99 (95% CI, 0.96 to 1.03) associated with each 5% decrease from baseline.

Post Hoc Analyses

Treating age as a continuous covariate, we did not find an exposure threshold for absolute MAP or largest percentage MAP reduction and AKI by adding spline terms at the 10th, 50th, and 90th exposure percentiles (Supplemental Digital Content fig. 1, http://links.lww.com/ALN/C751). We also did not find a different relationship between both exposures and outcome across sites from multivariable logistic regression treating age as a continuous covariate for confounders.

The sensitivity analysis, additionally adjusting for intraoperative blood loss, had results similar to the primary analysis, with an estimated adjusted odds ratio of 1.00 (95%

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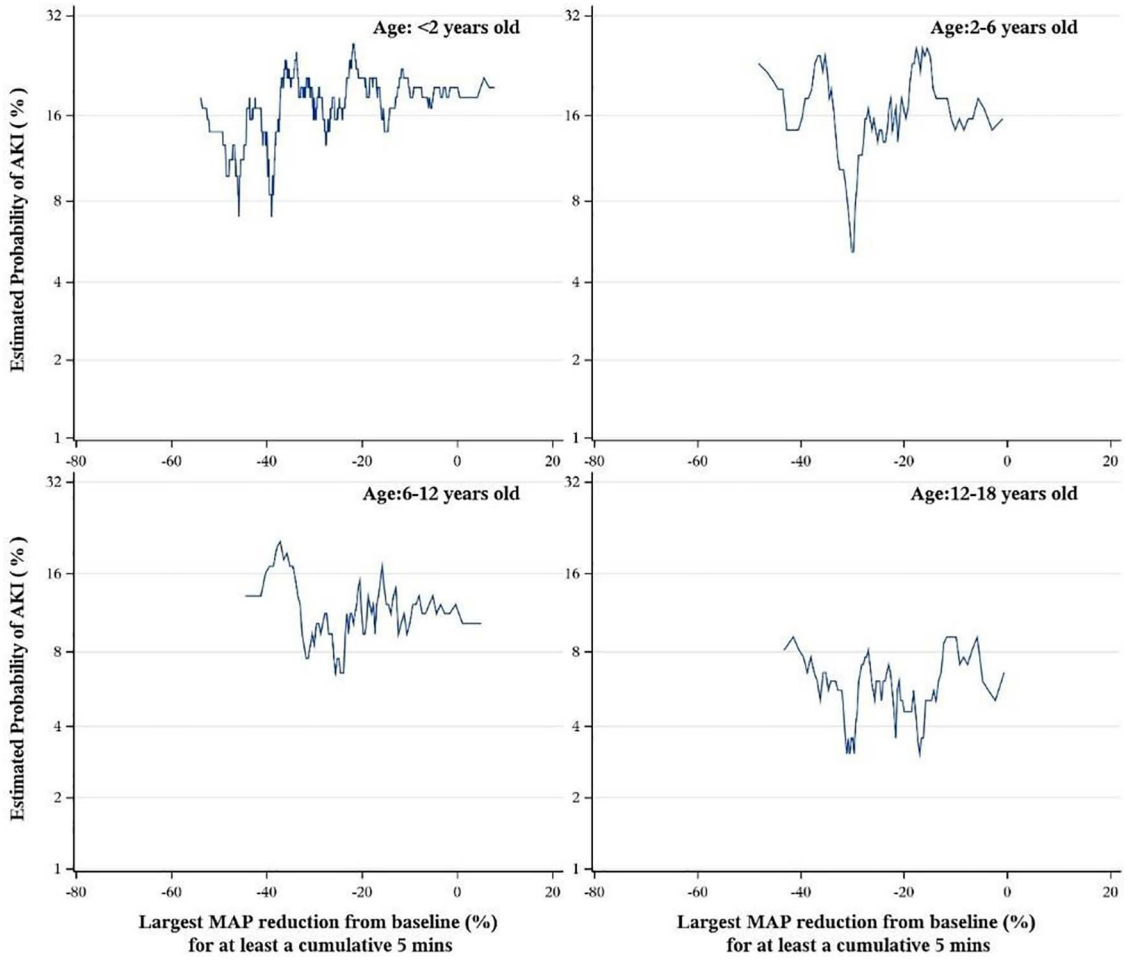

Fig. 3. Smooth moving average plot of risk of acute kidney injury (AKI) and largest mean arterial pressure (MAP) reduction from baseline (%) for at least a cumulative 5 min—all patients.

CI, 0.89 to 1.15) associated with each 5-mmHg decrease in lowest MAP. The result of the largest percentage MAP reduction from baseline was slightly different from the primary analysis with an estimated adjusted odds ratio of 1.02 (95% CI, 0.95 to 1.09) associated with each 5% decrease from baseline, but still failed to show a significant association between largest MAP reduction from baseline and postoperative AKI.

Discussion

The overall incidence of postoperative AKI among our pediatric surgical inpatients who had creatinine assessments was 11% (449 of 4,506). In contrast, Wingert *et al.* reported an incidence of AKI of only 3% in children having noncardiac surgery.[14] However, only 70% of patients in their cohort had general anesthesia, and they included shorter procedures, outpatient procedures, and only a third as many emergency operations.

The importance of baseline and procedural characteristics is illustrated by the striking difference in AKI incidence at Children's Health, 395 of 2,182 (18%), and the Cleveland Clinic, 104 of 2,324 (4.5%). The higher incidence at Children's Health presumably reflected more emergency surgery, more patients designated ASA Physical Status III or greater, and more preexisting hypertension. Nonetheless, no interaction by site was seen in the *post hoc* analysis.

Younger children had a higher incidence of AKI: for example, children under 6 yr old had an AKI incidence of 17% (258 of 1,484), children 6 to 12 yr had an incidence of 11% (122 of 1,062), and adolescents had an incidence similar to that reported in adult studies, about 6% (119 of 1,960).[6,15,16] This may reflect an intrinsic vulnerability, but may well be due to measurement bias since blood sampling is sometimes challenging in younger children—leading to preferential sampling in sicker patients. Age dependence of AKI is consistent with a report that the incidence is 34% in neonates having abdominal or thoracic surgical

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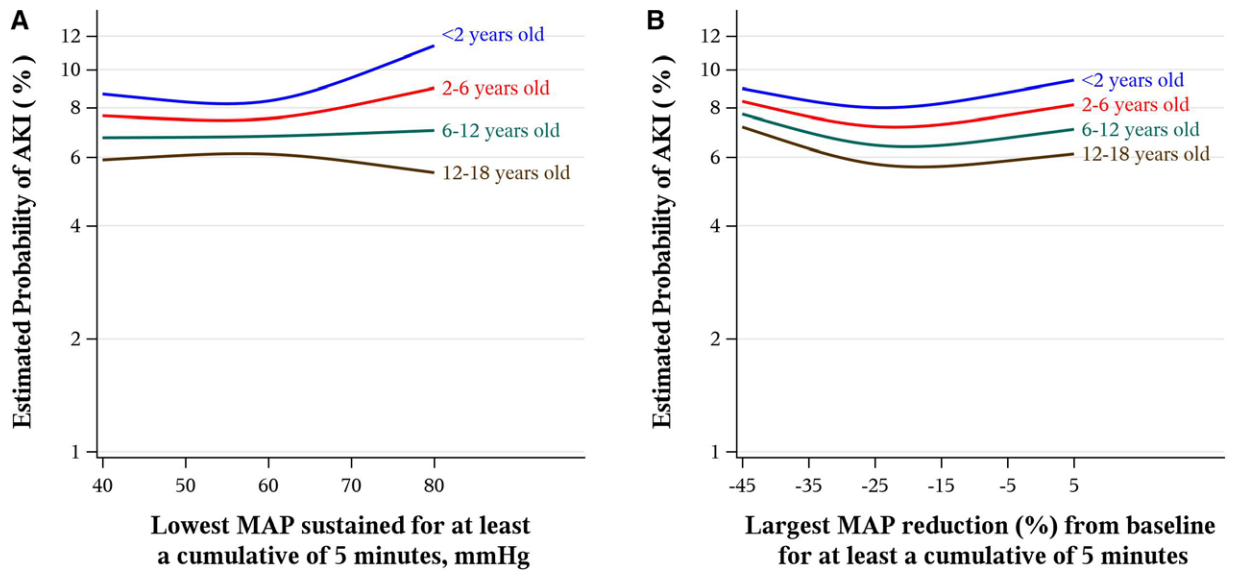

Fig. 4. The adjusted relationship between lowest mean arterial pressure (MAP) or MAP reduction and acute kidney injury (AKI) by age group. The associations between lowest MAP (*A*) or largest MAP reduction (*B*) and AKI were plotted by using a logistic regression model with natural cubic splines of exposure at the 10th, 50th, and 90th percentiles and interaction between age group and exposure spline, adjusting for confounders. The predicted probability of AKI was displayed for the patients with the mean values of confounders in the model. The *x*-axis range was chosen based on 5 to 95% of corresponding exposures.

Table 2. Associations between Lowest MAP or Largest Percentage MAP Reduction from Baseline and AKI

	Unadjusted		Adjusted	
	Estimated Odds Ratio (95% CI)	*P* Value	Estimated Odds Ratio (95% CI)*†‡	*P* Value
Lowest MAP, mmHg	1.00 (0.97–1.05)	0.814	0.99 (0.94–1.05)	0.856
Largest MAP reduction from baseline, %	1.01 (0.98–1.04)	0.513	1.00 (0.97–1.03)	0.997

The estimated odds ratio was obtained from univariate (unadjusted) and multivariable (adjusted) logistic regression models.

*Multivariable logistic regression model adjusted for confounders including sex, race, weight, American Society of Anesthesiologists Physical Status, site, preoperative tacrolimus or cyclosporine or furosemide use, organ transplant history, preoperative hemoglobin, preoperative comorbidities (obesity, liver disease, chronic pulmonary disease, hypertension, fluid and electrolyte disorder, chronic blood loss anemia, and deficiency anemias), surgery type, emergent surgery, intraoperative use of intravenous contrast material or ketorolac use or norepinephrine use or ephedrine use or crystalloid or gentamycin use or vancomycin use. For model with exposure of lowest MAP, baseline MAP was additionally adjusted for. †The interaction between lowest MAP and age group was not significant with $P = 0.856$. The interaction between largest MAP reduction from baseline and age group was not significant with $P = 0.978$. Thus, both interaction terms were dropped from the multivariable models to assess adjusted odds ratio. ‡Odds ratios: odds ratio of AKI associated with each 5-mmHg decrease in lowest MAP or each 5% decrease in largest MAP reduction from baseline.

AKI, acute kidney injury; MAP, mean arterial pressure.

procedures.[13] Only a very small fraction of our patients were neonates; consequently, our results are noninformative for this unique age group.

Currently, there is no consensus definition of hypotension in pediatric anesthesia. In adults, harm accrues at the extremes. Consequently, it is not the average MAP that matters; instead, it is the few minutes of extreme hypotension. Therefore, we defined hypotension by absolute (lowest MAP) or relative (largest MAP reduction) sustained for at least 5 cumulative minutes.

In distinct contrast to adults, where there are relatively clear absolute and relative thresholds associated with renal injury, there was no apparent threshold over the observed range of pressures. Thus, even strikingly low minimum pressures were not associated with AKI. Our results are consistent with a recent single-center study that also observed no significant confounder-adjusted association between intraoperative hypotension and AKI, with hypotension defined by MAP at least 1 SD below age- and sex-adjusted means.[14]

AKI was the only outcome we considered, but Gleich *et al.* report lack of association between intraoperative hypotension and poor neurodevelopmental outcomes in children less than 3 yr of age who had multiple general anesthesia

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exposures.[17] Surely there are degrees of hypotension that provoke organ injury in pediatric surgical patients, but our results suggest that children are relatively resistant to intraoperative hypotension, a conclusion that contrasts markedly with adults who appear sensitive to even modest degrees of hypotension. Renal resilience to hypotension in children may result from effective autoregulatory mechanisms. The theory is consistent with impairments in renal autoregulation consequent to chronic arterial hypertension,[18] generalized atherosclerosis,[19] and type 2 diabetes mellitus[20]—all of which are rare in children and common in adults.

Confounding and bias are inherent limitations of any observational analysis despite our efforts to adjust for potential confounders. However, confounding would more likely generate false harm thresholds than explain an apparent absence of a relationship between hypotension and renal injury. Despite being able to include fewer patients than anticipated, our statistical power remained excellent because the AKI incidence was higher than anticipated. Our study population was restricted to children who had creatinine measurements preoperatively and postoperatively, presumably explaining the high incidence of AKI. The incidence in the patients we report should therefore not be taken as the overall incidence in pediatric surgical patients, which is surely lower. Additionally, excluding patients for missing data (fig. 1) can bias the results in several ways.

Most children had intraoperative blood pressure assessed noninvasively (3,282 of 4,506; 73%; table 1). We do not have data on whether the measurement was taken by arm or calf, a limitation to our study results since MAP measurements may differ, especially in young children. Finally, we included only the creatinine component of the Kidney Disease Improving Global Outcomes AKI definition. It is probable that some additional AKI would have been identified had we been able to accurately assess urine output. However, it seems unlikely that including the urine output component of AKI would change our overall conclusion that there is little if any relationship between hypotension and AKI in children.

Only two tertiary centers participated, but it seems unlikely that hypotension would be meaningfully related to AKI in healthier patients having smaller operations. We included fewer patients than previous analyses in adults; nonetheless, our results are robust, and the lack of association between hypotension and AKI is not simply consequent to inadequate statistical power.

In summary, in distinct contrast to adults, we did not find any association between intraoperative hypotension as defined in this article and postoperative AKI. Hypotension may contribute to injury of other organs, and at some level presumably causes AKI. Nonetheless, our results suggest that short durations of hypotension should not be clinicians' primary concern when trying to prevent intraoperative renal injury in pediatric patients.

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Competing Interests

Dr. Sessler is a consultant for Edwards Lifesciences (Irving, California), Sensifree (Cupertino, California), and Perceptive Medical (Newport Beach, California). The other authors declare no competing interests.

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