Objectives: Hypotension thresholds that provoke renal injury, myocardial injury, and mortality in critical care patients remain unknown. We primarily sought to determine the relationship between hypotension and a composite of myocardial injury (troponin T ≥ 0.03 ng/mL without nonischemic cause) and death up to 7 postoperative days. Secondarily, we considered acute kidney injury (creatinine concentration ≥ 0.3 mg/dL or 1.5 times baseline).

Design: Retrospective cohort.

Setting: Surgical ICU at an academic medical center.

Patients: Two-thousand eight-hundred thirty-three postoperative patients admitted to the surgical ICU.

Interventions: A Cox proportional hazard survival model was used to assess the association between lowest mean arterial pressure on each intensive care day, considered as a time-varying covariate, and outcomes. In sensitivity analyses hypotension defined as pressures less than 80 mm Hg and 70 mm Hg were also considered.

Measurements and Main Results: There was a strong nonlinear (quadratic) association between the lowest mean arterial pressure and the primary outcome of myocardial injury after noncardiac surgery or mortality, with estimated risk increasing at lower pressures. The risk of myocardial injury after noncardiac surgery or mortality was an estimated 23% higher at the 25th percentile (78 mm Hg) of lowest mean arterial pressure compared with at the median of 87 mm Hg, with adjusted hazard ratio (95% CI) of 1.23 (1.12–1.35; p < 0.001). Overall results were generally similar in sensitivity analyses based on every hour of mean arterial pressure less than 80 mm Hg and any mean arterial pressure less than 70 mm Hg. Post hoc analyses showed that the relationship between ICU hypotension and outcomes depended on the amount of intraoperative hypotension. The risk of acute kidney injury increased over a range of minimum daily pressures from 110 mm Hg to 50 mm Hg, with an adjusted hazard ratio of 1.27 (95% CI, 1.18–1.37; p < 0.001).

Conclusions: Increasing amounts of hypotension (defined by lowest mean arterial pressures per day) were strongly associated with myocardial injury, mortality, and renal injury in postoperative critical care patients. (Crit Care Med 2019; 47:910–917)

Key Words: hypotension; intensive care; mean arterial pressure; outcomes; postoperative; surgical

Myocardial injury is the leading cause of attributable death after noncardiac surgery, accounting for about a quarter of all 30-day mortality (1). Acute kidney injury (AKI) also causes considerable morbidity and is associated with prolong hospitalization and mortality (2, 3).
Intraoperative hypotension is strongly associated with myocardial injury after noncardiac surgery (MINS) and death, and somewhat less strongly with kidney injury (4, 5). For example, only a few minutes of exposure to a mean arterial pressure (MAP) of 55 mm Hg is significantly associated with both MINS and death (6).

A difficulty is that most patients who become hypotensive postoperatively are also hypotensive intraoperatively, making it challenging to distinguish the relative contributions of intraoperative hypotension which can be profound but is usually short-lived from postoperative hypotension which is generally less severe but often prolonged. There is nonetheless evidence that postoperative ward hypotension is independently associated with a composite of myocardial infarction (MI) and death (7).

Critical care patients are especially likely to become hypotensive because of acute instability, and they are presumably especially likely to develop myocardial and renal injury because of high baseline risk. These patients are also susceptible to organ injury from the cumulative insults that intensive care patients so often experience. Intensivists thus appropriately focus on hemodynamic management and try to maintain a reasonable blood pressure without giving excessive fluid or vasopressor medications. Curiously, given how important blood pressure and perfusion are for organ function, there is limited evidence to suggest what lower limits might be safe (8–13)—and almost no evidence specific to myocardial and renal injury.

We therefore sought to assess what levels and durations of critical care MAP are associated with 1) a composite of in-ICU myocardial injury (troponin T ≥ 0.03 ng/mL without nonischemic cause) and death and 2) AKI. Our analysis was restricted to the initial 7 postoperative days in patients admitted to a surgical ICU (SICU) and was adjusted for the amount of intraoperative hypotension.

**MATERIALS AND METHODS**

With Institutional Review Board approval and waived consent, data from patients who had noncardiac surgery at the Cleveland Clinic Main Campus between 2009 and 2016 were obtained from the Anesthesia Institute's Perioperative Health Documentation System database and electronic medical record system. Our retrospective analysis was thus based on registry data. We included adults admitted to the SICU immediately after surgery and who stayed in the unit at least 24 hours.

We excluded patients who had kidney procedures including renal transplantation, nephrectomy, nephroureterectomy, or surgical relief of an obstructive uropathy. We similarly excluded patients with preexisting severe chronic kidney disease (defined as preoperative dialysis or an estimated glomerular filtration rate < 30 mL·min⁻¹) or with a preoperative troponin concentration greater than or equal to 0.03 ng/mL. We also excluded patients with missing type of surgery or missing preoperative creatinine concentration. Patients without adequate blood pressure measurements, including those with less than one recorded blood pressure value per hour or with any reading gaps longer than 2 hours, were excluded as well. Only the most recent surgery was considered for patients who had multiple operations. And finally, patients who had new-onset myocardial, renal injury, or death on the day of ICU admission were excluded.

**Measurements**

Baseline information included patients' age, sex, race, body mass index, ASA physical status, medical history, preoperative medications, and preoperative labs.

Intraoperative data included type of surgical procedure by organ (grouped by Clinical Classifications Software), medications, fluid administration (total amounts of crystalloid, colloid, and transfused blood), estimated blood loss, use of vasoressors, time-weighted average MAP, and the duration of the surgery. Missing variables were imputed using the median when the fraction was less than 2%. MAP was recorded at 1-min intervals for patients with an arterial catheter and every 1 to 5 minutes for those with noninvasive blood pressure monitoring in the operating room. All intraoperative MAP data was retrieved from anesthesia automated record keeping system (Talis Clinical, Streetsboro, OH).

ICU data included blood pressure, laboratory values, and relevant medications. We retrieved all blood pressure measurements during the initial ICU stay through unit discharge or the seventh postoperative day. Only nurse-verified blood pressures were included in the analysis. These were normally obtained at least hourly from an invasive arterial catheter or a noninvasive blood pressure cuff. For the primary exposure variable, the lowest MAP per day was summarized for each patient as a daily measure of hypotension severity. As sensitivity analyses, we planned to measure the burden of hypotension using two cut-off values of MAP, below 80 mm Hg or below 70 mm Hg. We found that 55% of patients had at least some time with MAP less than 80 mm Hg so that we used the cumulative duration of MAP less than 80 mm Hg as a continuous measurement of mild hypotension. Since only 20% of patients had any MAP less than 70 mm Hg during their ICU stay, we used a binary variable indicating whether a patient had any MAP less than 70 mm Hg or not. Data were retrieved from EPIC (Epic Systems Corporation, Verona, WI) and values of MAP less than 25 mm Hg or greater than 250 mm Hg were assumed to be errors and excluded from analysis.

Our primary outcome was a collapsed composite of in-ICU myocardial injury (MINS, defined as troponin ≥ 0.03 ng/mL without apparent nonischemic cause) and death within 7 postoperative days (14). Patients who had either MINS and or mortality (MINS/mortality) were identified as having the event. Detection of myocardial injury was assigned to the time of the first blood test with an elevated troponin concentration.

Our secondary outcome was in-ICU AKI, defined as per the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (including stages 1 to 3), during the initial 7 postoperative days. Baseline serum creatinine was measured as the average of serum creatinine values within the 7 days immediately preceding surgery (15). Renal injury (at any particular stage) was assigned to the first time blood was sampled with a qualifying creatinine concentration.
**Statistical Analysis**

Patients who had earlier postoperative complications were less likely to experience low blood pressure since exposure periods were shorter than in patients without any complications (16). To address this time-related bias, we used the lowest MAP on each day during the ICU stay as a time-varying covariate in a Cox proportional hazards survival model of time to first of either detection of MINS or mortality in the ICU, the primary outcome (12). Furthermore, as patients are usually discharged alive from the ICU due to amelioration of their condition, ICU discharge cannot be considered to be noninformative censoring in the survival analysis. Instead, we defined being discharged alive from ICU as a competing risk (17,18). For patients experiencing MINS or mortality in the ICU within 7 days of surgery, we used the earliest time of MINS/mortality as their event time, with no competing risk; patients who did not experience the composite outcome and were discharged within 7 days of surgery were coded as having a competing risk at their ICU discharge day; patients who did not experience the composite outcome and were still in the ICU at postoperative day 7 were censored at that time. Lowest MAP on each day was treated as a time-varying covariate; baseline-confounding variables were treated as fixed covariates. The cause-specific hazard ratio (HR) and 95% CI assessing the association between hypotension and the primary composite outcome was reported as the main effect estimate.

As the association between the lowest MAP and the hazard can be nonlinear overall, we added a quadratic term of lowest MAP to the model (i.e., linear + quadratic terms). If the added quadratic term was significant ($p < 0.05$) and therefore improved model fit, we would keep the quadratic term and report the cause-specific HR of MINS/mortality compared with various MAP levels to the median lowest MAP. Otherwise, we planned to report the linear relationship between lowest MAP and outcome with a single HR. All variables in Appendix Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/E519), except for the use of vasopressors in the ICU, (Supplemental Digital Content 1, http://links.lww.com/CCM/E519), were considered as potential confounders and were added to the model if univariate $p$ value was less than 0.25, and retained in backward elimination when $p$ value was less than 0.20. The selected confounders for primary and secondary outcomes are listed in Appendix Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/E519).

Secondarily, for the AKI analysis we used the earliest time of creatinine concentration greater than or equal to 0.3 mg/dL or 1.5 times higher than baseline as the outcome event time and the lowest MAP each day during ICU stay as exposure to assess the adjusted association of the lowest MAP on each day before development of AKI in a time-varying covariate Cox model using the same method described in primary analysis. Death or ICU discharge within 7 days were treated as competing risk factors as above. Patients who did not experience AKI and were still alive in the ICU were censored at postoperative day 7. The cause-specific HR of AKI was reported. Because the prognostic importance of perioperative stage 1 AKI remains unclear, we conducted a sensitivity analysis defining AKI as stage 2 or 3.

In a sensitivity analysis, we used different measurements to quantify ICU hypotension. Since 55% of patients had some time with MAP less than 80 mm Hg, whereas only 20% of patients had any MAP less than 70 mm Hg during their ICU stay, we chose the cumulative hours of MAP less than 80 mm Hg or any MAP lower than 70 mm Hg on each day as exposure variables and assessed their respective associations with postoperative MINS/mortality and AKI in a time-varying covariate survival model similarly as in the primary and secondary analyses. Furthermore, in another sensitivity analysis designed to capture patients who did not have the primary outcome and were discharged from the ICU before 7 postoperative days, we re-defined the timing of the primary outcome and expanded the study period to include hospital stay within 7 days. Hospital discharge within 7 days was treated as a competing risk factor. Missing MAP due to ICU discharge was set as “last value carried forward,” replaced by the values from the last day of ICU stay. The cause-specific HR was reported to assess the association with the outcomes.

In post hoc analyses, we assessed the interaction between several pre-ICU variables and lowest MAP versus outcome, including age, history of MI, preoperative MAP, and intraoperative area under the curve (AUC) of MAP less than 65 mm Hg using the same methods as described for the primary analyses. Interaction $p$ values of less than 0.10 were considered significant.

### TABLE 1. Associations Between Lowest Mean Arterial Pressure Per Day and 7-Day Postoperative Complications in Surgical ICU

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incidence</th>
<th>Hazard Ratio (95% CI)*</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td>Comparing to median (87 mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Myocardial injury after noncardiac surgery/mortality</td>
<td>98 (3.5%)</td>
<td>Fifth percentile (67 mm Hg)</td>
<td>1.67 (1.26–2.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25th percentile (78 mm Hg)</td>
<td>1.23 (1.12–1.355)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75th percentile (98 mm Hg)</td>
<td>0.88 (0.79–0.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95th percentile (109 mm Hg)</td>
<td>0.88 (0.64–1.23)</td>
</tr>
</tbody>
</table>

Secondary outcome

| Acute kidney injury | 405 (15%) | 10 mm Hg decrease | 1.27 (1.18–1.37) | $<0.001^b$ |

*The cause-specific hazard ratios of myocardial injury after noncardiac surgery/mortality with ICU discharge as competing risk and acute kidney injury with ICU discharge and death as competing risks were estimated using time-varying covariate Cox proportional hazard model with hospital discharge as competing risk, adjusted for selected potential confounders listed in Appendix Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/E519).

*Indicates that the association is statistically significant.
statistically significant. For all other analyses, we used a signif-
icance criterion of 0.05 and a corresponding 95% CI. All tests
were two-sided. SAS Version 9.4 (SAS Institute, Cary, NC) was
used for all analyses.

RESULTS
Two-thousand eight-hundred thirty-three patients met all
inclusion and exclusion criteria for the primary composite
outcome of MINS/mortality and the secondary outcome of
AKI (Fig. 1). After excluding patients with the outcome of
interest on the same day of SICU admission, 2,766 patients
were included in the primary analysis. Ninety-eight patients
(Table 1) experienced the primary outcome of MINS/mor-
tality in the ICU and 48 after ICU discharge, for a total of 146
patients (Appendix Table 2, Supplemental Digital Content
2, http://links.lww.com/CCM/E520) during the initial 7 days
after the surgery. Among those 98 patients with MINS/mor-
tality, 84 (3.0%) had MINS
and 17 (0.6%) died in the ICU
(three patients had MINS be-
fore they died). Patient char-
acteristics were summarized
by whether or not they had the
primary outcomes of MINS/
mortality (Appendix Table 1,
Supplemental Digital Content
1, http://links.lww.com/CCM/
E519), as well as by whether
or not they had the secondary
outcome of AKI (Appendix
Table 3, Supplemental Digital
com/CCM/E521).

Adding a quadratic term
improved model fit for in-
ICU MINS/mortality. We
thus reported the HR at vari-
ous values of the exposure
compared with the median
lowest MAP of 87 mm Hg,
adjusted for potential con-
founders listed in Appendix
Table 4 (Supplemental Digital
com/CCM/E522). The lower
quartile (across all days) of
lowest MAP of 78 mm Hg was
significantly associated with
higher hazard of MINS/mor-
tality (first occurrence of any)
compared with the median of
87 mm Hg. The adjusted HR
of MINS/mortality was 1.23
(95% CI, 1.12–1.35; \( p = 0.001 \)),
meaning that patients with
lowest daily MAP at 78 mm
Hg had an estimated 23% in-
crease in the chance of having
an event at any time given that
they did not have an earlier
event (i.e., given that they are
still in the risk set) (Fig. 2,
A and B, and Table 1) compared
with the patients with lowest

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**Figure 1.** Flow chart depicting inclusion and exclusion criteria and patient distribution for the study.
SICU = surgical ICU.
daily MAP at 87 mm Hg. Comparing the upper quartile of 98 mm Hg for lowest MAP to the median, the association between lowest MAP and outcome was not significant, with an estimated HR of 0.88 (95% CI, 0.79–0.99; \( p = 0.095 \)) (Fig. 2, A and B and Table 1).

The relationship between lowest daily MAP in the ICU and the composite outcome depended on amount of intraoperative hypotension as well as on history of MI. For patients with a low level of intraoperative hypotension (AUC of MAP < 65 < 2 mm Hg × hr), duration of ICU MAP less than 80 mm Hg (interaction \( p = 0.10 \)), and lowest ICU MAP (interaction \( p = 0.29 \)) were associated with higher MINS/mortality (\( p < 0.001 \)), but for those with higher levels of intraoperative hypotension there was no relationship between outcome and ICU hypotension. In patients with history of MI there was a significant interaction between duration of ICU MAP less than 80 mm Hg (interaction \( p = 0.06 \)) and outcome, but not for lowest MAP (interaction \( p = 0.33 \)).

Secondarily, we analyzed the association between hypotension and in-ICU AKI among 2,737 patients by excluding cases of AKI, which occurred the day of SICU admission, again adjusted for confounders listed in Appendix Table 4 (Supplemental Digital Content 4, http://links.lww.com/CCM/E522). Four-hundred five patients (15%) had AKI in the ICU (Table 1), and 133 experienced AKI after ICU discharge for a total of 538 patients (Appendix Table 2, Supplemental Digital Content 2, http://links.lww.com/CCM/E520), during the initial 7 days after the surgery based on their creatinine level.

Quadratic form of lowest MAP models were not added because it was not significantly associated with AKI (\( p = 0.80 \)) and it did not improve model fitting. The adjusted HR of AKI associated with a 10 mm Hg decrease in lowest MAP was 1.27 (95% CI, 1.18–1.36; \( p < 0.001 \)) (Fig. 2C) and Table 1). Of patients in the ICU, 4.8% experienced stage 2-3 AKI. Using this definition, the HR for a 10 mm Hg decrease in lowest daily MAP was 1.35 (95% CI, 1.19–1.54; \( p < 0.001 \)). The association between hypotension and severe AKI was thus slightly stronger than that for all AKI.

We conducted a sensitivity analysis using the cumulative hours of MAP less than 80 mm Hg during each day as the exposure. The duration of hypotension was significantly associated with increased hazard of in-ICU MINS/mortality. As shown in Table 2, a 1-hour increase (i.e., difference between patients) in hypotension duration (at a MAP < 80 mm Hg) was significantly associated with MINS/mortality (HR, 1.09; 95% CI, 1.02–1.17; \( p = 0.009 \)) and with AKI as well (HR, 1.19; 95% CI, 1.06–1.13; \( p < 0.001 \)). Furthermore, when comparing patients with any MAP less than 70 mm Hg with patients without it for each day, the estimated HR of MINS/mortality was 1.80 (95% CI, 1.05–3.09; \( p = 0.033 \)) and the HR of AKI was 1.91 (95% CI, 1.46–2.50; \( p < 0.001 \)), showing in general that exposure to MAP less than 70 mm Hg was significantly associated with both of the outcomes. The sensitivity analyses were adjusted for confounders listed in Appendix Table 4 (Supplemental Digital Content 4, http://links.lww.com/CCM/E522) for both MINS/mortality and AKI.

Furthermore, when considering an additional sensitivity analysis to include all in-hospital postoperative complications within 7 days, we found lowest MAP was similarly associated with both MINS/mortality and AKI, as shown in Appendix Table 2 (Supplemental Digital Content 2, http://links.lww.com/CCM/E520). The hazard of MINS/mortality was significantly greater for patients having lowest MAP of 78 mm Hg (first quartile), comparing to a median lowest MAP of 87 mm Hg, adjusted for confounders in Appendix Table 4 (Supplemental Digital Content 4, http://links.lww.com/CCM/E522), with a HR of 1.20 (95% CI, 1.09–1.32; \( p < 0.001 \)). Patients with lowest MAP of 98 mm Hg (third quartile) did not have a significantly lower hazard of MINS/mortality compared with the median lowest MAP of 87 mm Hg (HR, 0.90; 95% CI, 0.81–1.01; \( p = 0.076 \)). MAP was significantly associated with AKI as well,
with a HR of 1.22 (95% CI, 1.14–1.30; \( p < 0.001 \)) per 10 mm Hg decrease in lowest MAP on each day during ICU stay.

**DISCUSSION**

In our postoperative critical care population, there was a strong association between a lowest median MAP on each ICU day and the primary outcome, a composite of MINS and mortality. Because the relationship is quadratic, no single HR applies throughout. But for example, risk increased 23% when comparing the median lowest pressure of 87 mm Hg to the 25th percentile lowest pressure of 78 mm Hg. At lower pressure ranges, the same 9 mm Hg difference in lowest minimum pressure on a given day further increased hazard. We found a significant interaction between intraoperative hypotension and ICU hypotension related outcomes. Consequently, a specific threshold MAP in postoperative critical care patients with an independent association with outcomes could not be identified.

Intraoperative threshold MAPs associated with organ system injury have been identified to be roughly 65 mm Hg (4, 6). Our analysis suggests that there were an increasing hazards of harm associated with lowest MAPs in the surgical postoperative ICU at pressures much higher than 65 mm Hg. Most likely, the intraoperative threshold is low because general anesthesia reduces metabolic rate about 30%, which in turn reduces metabolic demand and perfusion requirements (19). On the other hand, postoperative critical care patients may have had several coexisting insults, received vasopressors, have major fluid shifts, and preexisting and surgical organ system injury. Additionally, some were febrile which further augments metabolic rate and perfusion requirements.

The Surviving Sepsis Guidelines recommend titrating vasopressors to a minimum MAP target of 65 mm Hg (20). However, the level of evidence supporting this recommendation is moderate at best and is largely supported by trials that have shown fewer cardiac arrhythmias, less vasopressor use, and similar mortality at higher and lower MAP targets (21–23).

For example, the largest trial supporting the Surviving Sepsis blood pressure guidelines randomized 776 patients to high (80–85 mm Hg) versus low (65–70 mm Hg) MAP targets for vasopressor therapy in vasodilatory septic shock (24). In fact, pressures in the two groups were 70–75 mm Hg versus 85–90 mm Hg. There were no significant differences in cardiac arrhythmias (20% vs 36%; \( p = 0.07 \)) and hospital mortality (30% vs 33%; \( p = 0.84 \)). The study was underpowered for rare outcomes such as myocardial infarction and infarction, which were observed in only two and seven patients in the low and high MAP target groups, respectively. In addition, the trial was underpowered for mortality (25). Interpretation is further complicated because myocardial injury (troponin > 0.03 ng/mL in the absence of nonischemic cause) was not identified separately from clinical MI.

There have also been previous observational studies in non-surgical critical care patients that identified MAP thresholds for AKI and mortality ranging between 65 and 82 mm Hg (8–10, 26, 27). However, these studies were smaller than ours and included a heterogeneous septic shock population. Population matters since hypotension is essential for a diagnosis of septic shock, which in itself may cause AKI, and myocardial injury; septic shock is thus both a mediator and confounder (28). In contrast, our patients were directly admitted from the operating room after elective surgery and therefore presumably rarely septic during our 7-day observation period. Additionally, we considered myocardial injury that is more common than clinically apparent MI and mortality. MINS and silent troponin elevations are as serious as infarctions meeting the third Universal Definition of Myocardial Infarction with a 30-day mortality of 4% (1).

Importantly, recently Maheshwari et al (29) identified that risks for mortality, AKI, and myocardial injury were first apparent at a MAP of 85 mm Hg in ICU patients with septic shock. Further, as in our population, there was a progressive increase in the risk for mortality and AKI as the MAP decreased from 85 to 55 mm Hg.

We also saw an association between MAP and AKI from 50 to 110 mm Hg. This relationship was linear and differed from quadratic relationship between MINS and hypotension. Therefore, there was a single HR of 1.27 or a near 30% increase

### Table 2. Sensitivity Analysis on Primary (Myocardial Injury After Noncardiac Surgery/Mortality) and Secondary Outcomes (Acute Kidney Injury)

<table>
<thead>
<tr>
<th>MAP Measurement</th>
<th>Outcomes</th>
<th>Hazard Ratio (95% CI)</th>
<th>Per 1 hrb</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative duration of MAP under 80 mm Hg</td>
<td>MINS/mortality</td>
<td>1.09 (1.02–1.17)</td>
<td>&lt;0.001c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AKI</td>
<td>1.09 (1.06–1.13)</td>
<td>&lt;0.001c</td>
<td></td>
</tr>
<tr>
<td>Any MAP under 70 mm Hg</td>
<td>MINS/mortality</td>
<td>1.80 (1.05–3.09)</td>
<td>0.033c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AKI</td>
<td>1.91 (1.46–2.50)</td>
<td>&lt;0.001c</td>
<td></td>
</tr>
</tbody>
</table>

AKI = acute kidney injury, MAP = mean arterial pressure, MINS = myocardial injury after noncardiac surgery.

*The cause-specific hazard ratios of MINS/mortality with ICU discharge as competing risk and AKI with ICU discharge and death as competing risks were estimated using time-varying covariate Cox proportional hazard model, adjusted for selected potential confounders listed in Appendix Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/E519).

Adjusted hazard ratio for 1 hr increase of MAP < 80 mm Hg on each day.

Indicates that the association is statistically significant.

Adjusted hazard ratio comparing patients with vs without MAP < 70 mm Hg on each day.

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in risk for AKI for lowest daily MAP values 10 mm Hg lower than other otherwise comparable patients in the ICU. Our results suggest that the kidneys remain very sensitive to the effects of hypotension and likely at higher thresholds than the myocardium as shown by other investigators (6, 24, 29).

The KDIGO guidelines technically define stage 1 as “risk” rather than injury. Indeed, the severity of AKI stage is independently associated with in hospital mortality in nonoperative patients (30). In our cohort, the association with hypotension was even stronger (HR 1.39 per 10 mm Hg) when the analysis was restricted to severe and obviously clinically important degrees of AKI (stages 2–3). Hypotension is thus strongly associated with degrees of AKI that are clearly clinically important.

Every 1 hour spent with a MAP less than 80 mm Hg and any duration of time at a MAP less than 70 mm Hg was significantly associated with MINS/mortality and AKI. Additionally, patients with any MAP less than 70 mm Hg had twice the risk of MINS/mortality. Our analysis was thus able to provide an estimate of a “hypotensive burden” and associated damage in a highly vulnerable critically ill postsurgical population. Another strength was that our cohort was more homogenous than a typical critical care population in that patients were all direct transfers from the operating room to the SICU. A natural consequence is that associations between hypotension and myocardial and renal injury may well differ in other types of intensive care patients, and even in surgical patients who remain in critical care beyond 7 days.

A complexity of critical care is that there is almost complete overlap between exposure and potential outcome periods. We thus used the lowest MAP every day in the SICU as a time-varying covariate in a Cox proportional hazards survival model for our analysis. Specifically, we considered blood pressure measurements only until an event was recorded, or until the study ended 7 days postoperatively.

Our analysis has the inherent limitations of any retrospective study design. First, although we controlled for an exhaustive list of known potential confounders, it remains possible that hypotensive patients had worse outcomes because they were sicker in ways that we could not adjust for. To the extent that this sort of confounding contributed, the observed associations may not be causal and thus unlikely to be improved by interventions to maintain higher mean pressures. Further, the absence of randomization in a complex population such as this means that these signals for harm at lower pressures are secondary to unknown confounding. The results should thus be interpreted with clinical caution. Second, our analysis was restricted to nurse-verified blood pressures, typically at 1-hour intervals. Possibly patients who were sicker, on vasoPressors, and had arterial catheters had more nurse-validated recordings per hour. Surely at least some patients had substantially worse hypotension between recorded measurements. Third, we were limited in the lack of availability of accurate hourly urine output data. We therefore considered only the creatinine component of the KDIGO renal injury criteria.

We used a 7-day cutoff period for postoperative patients, which may be considered arbitrary, although a reasonably long period for the exposure and outcome of interest. Many patients left the SICU before 7 postoperative days, specifically in our study, 86% patients were discharged early from the ICU to the floor. We assumed that these patients were hemodynamically stable and unlikely to experience critically low blood pressures, but clearly some ward patients have critically low pressures—sometimes for extended periods (7). Although, we did not have ward blood pressure data, there was a consistent and similar association both for our primary and secondary analyses (observation period limited to only ICU stay up to a maximum of 7 postoperative days) and an additional sensitivity analysis extending to in-hospital outcomes (observation period up to a maximum of 7 postoperative days including hospital stay). We used troponin measurements that were not mandated across the entire patient population and were presumably done more often on the sicker group, with likely more hypotension or more risk factors. And finally, the analysis and results did not make an inference about changes within a subject across days. The reported HR thus does not refer to blood pressure changing from day to day. Instead, we compared blood pressures across patients who reached a given day without having already experienced MINS/mortality or AKI. All of the data from each of the patients before they had their event was used in the estimation of the HR. The HR per 9 or 10 mm Hg MAP therefore refers to the difference between two otherwise comparable patients at a given time. Finally, we did adjust our model for intraoperative hypotension but found that an association of interest (intraoperative hypotension) had a significant interaction with our primary outcome of MINS/mortality. Although we could not estimate an independent association of ICU hypotension threshold and outcomes, our results make clinical sense in that surgical critical care patients often remain hypotensive in the ICU as a consequence of intraoperative hypotension.

CONCLUSIONS

In summary, even brief periods of hypotension as defined by lowest MAPs per day were associated with AKI and a composite of MINS/mortality within the initial 7 postoperative critical care days. This population appears to be especially sensitive to even mild amounts of hypotension. The interpretation of these data deserve caution, especially when extrapolating these to a nonsurgical septic population.

REFERENCES


