Perioperative myocardial injury and the contribution of hypotension

Daniel I. Sessler1* and Ashish K. Khanna1,2

© 2018 Springer-Verlag GmbH Germany, part of Springer Nature and ESICM

Abstract
Mortality in the month following surgery is about 1000 times greater than anesthesia-related intraoperative mortality, and myocardial injury appears to be the leading cause. There is currently no known safe prophylaxis for postoperative myocardial injury, but there are strong associations among hypotension and myocardial injury, renal injury, and death. During surgery, the harm threshold is a mean arterial pressure of about 65 mmHg. In critical care units, the threshold appears to be considerably greater, perhaps 90 mmHg. The threshold triggering injury on surgical wards remains unclear but may be in between. Much of the association between hypotension and serious complications surely results from residual confounding, but sparse randomized data suggest that at least some harm can be prevented by intervening to limit hypotension. Reducing hypotension may therefore improve perioperative outcomes.

Keywords: Anesthesia, Critical care, Blood pressure, Hypotension, Myocardial injury, Renal injury, Mortality

Introduction
In recent decades, anesthesia-related intraoperative mortality has decreased from roughly 1 in 10,000 patients to less than 1 in 100,000 patients, even though surgical patients are now far sicker than previously [1, 2]. In fact, intraoperative mortality is now so low that it is hard to quantify. In striking contrast, 30-day postoperative mortality is 1–2% [3, 4] and has only slightly improved over the last decade [5]. Postoperative mortality is thus about 1000 times more common than anesthesia-related intraoperative mortality. If mortality within 30 days after surgery were considered a disease, it would be the third leading cause of death in USA [6].

Postoperative myocardial injury
Inpatient surgery accounts for nearly all postoperative deaths, with an incidence of about 2% [7]. Half occur during the initial hospitalization, that is while patients remain under direct supervision in our highest-level healthcare facilities. Myocardial infarction is the leading cause of attributable postoperative death, accounting for a quarter of all mortality, far exceeding major bleeding (14%) and sepsis (9%). About 4% of surgical inpatients over the age of 45 years will have a myocardial infarction meeting the American Heart Association’s 3rd Universal Definition. About 18% will meet the definition of MINS, and 4% of those who do die within the month (adjusted hazard ratio 3.6). More than 90% of myocardial infarctions within the initial 30 postoperative days occur within 2 days after surgery [8].

Most postoperative myocardial injury is clinically silent and is only identified by routine troponin screening. More than 90% of patients who have troponin elevations apparently due to cardiac ischemia will have no symptoms whatsoever. Most also do not have electrocardiographic or echocardiographic evidence of ischemia and thus do not meet criteria for myocardial infarction specified in the 3rd Universal Definition. While it is tempting to dismiss asymptomatic troponin elevations as “troponitis,” mortality is almost as high without symptoms as with symptoms—indicating that isolated troponin elevations...
should be taken seriously [8]. Because troponin elevation with or without symptoms has comparable prognostic significance, it is referred to as myocardial injury after non-cardiac surgery, abbreviated MINS [9].

In the absence of consensus definitions, MINS is currently defined by postoperative troponin elevation that is apparently of cardiac origin [10]. The thresholds for MINS depend on the type of troponin. For fourth-generation troponin T, for example, MINS is defined by a postoperative concentration \( \geq 0.03 \) ng/ml. For fifth-generation (high sensitivity) troponin T, the threshold is: (1) a postoperative concentration \( \geq 20 \) ng/l with an increase from baseline of at least 5 ng/l, or (2) a postoperative concentration \( \geq 63 \) ng/l. Two days of postoperative monitoring will identify 90% of MINS and is thus usually sufficient. Unlike troponin T, which is a branded product that is similar worldwide, troponin I is generic and there are many versions, each with corresponding thresholds.

Nonoperative myocardial infarctions result largely from coronary plaque rupture. The etiology of postoperative myocardial infarctions remains poorly delineated, but supply-demand mismatch and coronary thrombosis appear to be important causes—although they rarely cause nonoperative infarctions. As with nonoperative infarctions, most do not display ST-segment elevation [11].

**Preventing postoperative myocardial infarction**

A large international prospective cohort study, VISION, demonstrated that more patients with MINS died than patients with other problems in the postoperative period [8]. Consequently, there have been substantive multinational efforts to test various prophylactic treatments for prevention of MINS.

The first major double-blinded randomized trial was POISE, which compared extended-release metoprolol and placebo in more than 8000 surgical inpatients at high cardiovascular risk [12]. Metoprolol 100 mg or placebo was given shortly before surgery and was followed by 200 mg/day or placebo for 30 days. The beta blocker reduced the incidence of myocardial injury by 30% which was highly statistically significant, and of course clinically important. However, beta blocker administration also caused serious hypotension and strokes, which increased overall mortality. Acute treatment with metoprolol thus failed to safely prevent postoperative myocardial infarctions. It is, of course, possible that lower doses or different beta blockers would work better, but such theories remain entirely speculative.

A second major randomized trial, ENIGMA-2, tested the hypothesis that avoiding nitrous oxide reduces the risk of cardiovascular complications. The basis for this theory is that nitrous oxide impairs vitamin B12 and folate metabolism, resulting in increased plasma homocysteine concentrations and impaired endothelial function. The assessor-blinded trial randomized 7000 high-risk surgical inpatients to 70% nitrous oxide or 70% nitrogen. There was no effect whatsoever of nitrous oxide on the primary composite of cardiovascular complications in either the entire population or any pre-defined subgroup. Also no toxicity was observed, except a modest increase in severe nausea and vomiting. Nitrous oxide thus appears to have neither positive nor negative effects on any substantive outcome.

The last major trial of prophylaxis for myocardial infarction was POISE-2, a double-blinded factorial trial of aspirin and clonidine [13]. Aspirin was included because its anti-platelet activity might reduce coronary thrombosis and because of its unquestioned role in preventing secondary infarction. (Whether aspirin is effective for primary prevention of myocardial infarction is less established.) Clonidine was included because many previous studies indicated that central alpha receptor agonists control heart rate without causing nearly as much hypotension as beta blockers.

POISE-2 randomized 10,010 multinational non-cardiac surgical inpatients who were at high cardiovascular risk. Aspirin did not reduce the risk of myocardial infarction or death within 30 days, but did increase the risk of major bleeding (Fig. 1a) [14]. Clonidine also failed to reduce the risk of myocardial infarction or death, while provoking clinically important hypotension and bradycardia (Fig. 1b) [15].

Beta blockers, avoiding nitrous oxide, aspirin, and clonidine, all failed to reduce risk, and three of the four drugs caused serious complications. There is thus currently no documented way of safely preventing myocardial infarction after surgery.

**Associations between intraoperative hypotension and myocardial and kidney injury**

Hemodynamic control has always been a goal of anesthetic management, but surprisingly little is known about optimal targets. Furthermore, much previous work focused on cerebral perfusion although the brain is probably less sensitive to hypotension than the heart and kidneys. One difficulty has been that until the relatively recent development of cardiac troponin, clinicians lacked sensitive biomarkers for myocardial injury. A second
difficulty is that reliably estimating associations between degrees of hypotension and various relatively rare outcomes requires accurate minute-by-minute details from tens of thousands of cases that were unavailable until electronic anesthesia records became routine.

Blood pressure is a complex signal that varies considerably over time and includes various components, including diastolic, mean, systolic, and pulse pressures [16, 17]. Unpublished analyses suggest that diastolic, mean, and systolic pressures from radial arterial catheters comparably predict perioperative myocardial and renal injury.

How best to characterize complex time-varying signals also remains unclear, and various "curve descriptors" have been used, including mean, time-weighted average, minimum, time under various thresholds, area under thresholds, time-weighted average under thresholds, minimum pressure maintained for various periods, etc. Associations between pressure and consequent outcomes will obviously depend on how blood pressure is characterized. However, simple characterizations such as mean and time-weighted average may be less useful than measures that quantify the duration and severity of pressures at the extremes which is where injury apparently occurs.

Recent work identifies strong associations between even brief periods of mild hypotension and myocardial injury, renal injury, and mortality [18, 19]. Concerningly, the harm thresholds appear to be high and include blood pressures that many anesthesiologists still routinely tolerate. There are now at least some randomized data suggesting that the relationship is causal and that intervening to limit hypotension reduces the risk of organ failure [20, 21].

There is a strong association between intraoperative hypotension and mortality [22]. Risk increases substantially when the minimum mean arterial pressure maintained for 10 min is less than about 70 mmHg (Fig. 2) [23]. There are similarly strong associations between hypotension and myocardial and kidney injury [24]. The threshold for myocardial injury is a mean arterial pressure of about 65 mmHg (Fig. 3a). The threshold for renal injury appears to be even greater, perhaps near 75 mmHg [24].

There are also strong associations between hypotension and myocardial (Fig. 3b) and renal injury when mean

Fig. 1. a, left: Kaplan-Meier estimates of the primary composite outcome of death or nonfatal myocardial infarction at 30 days in 10,010 patients randomized to aspirin or placebo. b, right: Kaplan-Meier estimates of the primary composite outcome of death or nonfatal myocardial infarction at 30 days in 10,010 patients randomized to clonidine or placebo. The inset for each shows the same data on an enlarged y axis. With permission from Devereaux and Sessler [11]: Clonidine in patients undergoing noncardiac surgery. N Engl J Med 2014; 370: 1504–1513

Fig. 2. Mortality in 30 postoperative days as a function of time-weighted average (TWA) mean arterial pressure or lowest mean pressure maintained for at least 10 min. With permission from Mascha et al. [23]: Intraoperative mean arterial pressure variability and 30-day mortality in patients having noncardiac surgery. Anesthesiology 2015; 123: 79–91
arterial pressure is expressed as a percentage of baseline clinic pressures. However, changes from baseline are not more predictive than an absolute threshold of 65 mmHg, which is easier to use clinically. The conclusion that absolute thresholds are usually sufficient is consistent with a previous report by Charlson and colleagues who demonstrated that the sensitivity, specificity, and prediction of complications was similar for 20% changes in mean arterial pressure and absolute 20 mmHg changes [17]. In contrast to blood pressure level, pressure variability is only weakly associated with adverse outcomes [4]. Intraoperative hypotension, defined by mean arterial pressure <70 mmHg, is also not associated with strokes [25]—although stroke risk surely increases at some pressure level.

In an analysis of adults having non-cardiac surgery at the Cleveland Clinic, a full third of all hypotension, defined by mean arterial pressure <65 mmHg, occurred between anesthetic induction and surgical incision. Furthermore, hypotensive minutes were significantly and comparably associated with both myocardial and kidney injury before and after incision (unpublished data). Aside from the occasional contribution of patient positioning, hypotension before incision results exclusively from anesthetic drugs. It is also largely preventable—and probably should be. One way to reduce intraoperative hypotension is to hold angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the day of surgery [26].

In contrast to blood pressure, tachycardia is either not associated with myocardial injury (unpublished data) or only associated at sustained rates exceeding 100 beats/min [10]. For example, Abbott and colleagues report that prolonged heart rate >100 bpm in combination with a systolic blood pressure <100 mmHg is associated with increased risk of MINS. They also showed that the lowest intraoperative heart rate >55 bpm and highest systolic pressure >160 mmHg was also associated with MINS. The analysis was limited by lack of continuous measurements of intraoperative heart rate and blood pressure [27].

A limitation of all observational data is that associations can be confounded by factors related to both exposure and outcome [28, 29]. For example, sicker patients are more likely to develop intraoperative hypotension and more likely to die. However, hypotension may simply be a marker of underlying illness rather than a mediator of harm. Similarly, patients who become hypotensive during surgery are also likely to become hypotensive postoperatively, and it might be the postoperative hypotension that causes harm.

Observational analyses routinely adjust for known confounders. But there are always residual confounding
factors that are unknown or poorly quantified, making it hard to estimate the extent to which confounding contributes to apparent associations. The distinction is important because associations that result from confounding will not be amenable to intervention. Most likely, intraoperative hypotension is both a marker of underlying illness and a mediator of organ injury. The only reliable way to distinguish the relative contributions of each mechanism is with an interventional trial. Fortunately, at least some randomized data are now available.

Futier and colleagues compared tight versus minimal intraoperative blood pressure control (n = 298) [20]. High-risk patients were randomized to minimal blood pressure control (ephedrine for systolic pressure < 80 mmHg or < 40% below baseline) versus a norepinephrine infusion to maintain systolic pressure within 10% of baseline values during and for 4 h after surgery. The primary outcome, a composite of systemic inflammatory response syndrome and/or at least one organ failure, occurred in 56/147 patients in the norepinephrine group versus 75/145 patients in the minimal control group: relative risk 0.73 [95% CI 0.56, 0.94]. The investigators also reported that there were fewer sepsis cases and that the duration of hospitalization was shorter with tight blood pressure control.

A notable aspect of the trial is that the intervention threshold in the minimal control group was quite low. Most anaesthetists intervene well before systolic pressure reaches 80 mmHg [30]. A higher intervention pressure presumably would have reduced the observed 25% benefit. The actual difference in mean pressure was small, just 6.5 mmHg. The investigators do not report the amount of hypotension below critical thresholds, which is probably when harm occurs.

Differences in the primary outcome were largely due to acute renal injury, which is understandable since the threshold for kidney injury appears to be higher than for myocardial injury, perhaps 75 mmHg rather than 65 mmHg [28, 29]. It is also consistent with previous trial evidence for an association between blood pressure control and acute renal injury [21]. The other substantive difference was in altered consciousness, which is somewhat surprising since autoregulation protects the brain at least from moderate hypotension. It also seems inconsistent with a recent trial in which blood pressure was titrated to maintain cerebral saturation and failed to identify a benefit during cardiac surgery [31]. Curiously, there was only one myocardial infarction identified in nearly 300 high-risk patients, despite routine troponin screening. Based on the VISION cohort [8], many more would be expected.

Available data suggest that even brief periods of mild intraoperative hypotension are harmful. Harm appears to start at mean arterial pressures near 65 mmHg. Myocardial and renal injury depends on the duration and severity of hypotension, with only a few minutes being required once mean pressure reaches 55 mmHg [32]. Of course hypotension-induced harm is not distributed randomly among surgical patients; harm is by far most likely in patients with pre-existing risk factors—especially cardiovascular disease.

**Ward hypotension and myocardial injury**
Intraoperative hypotension is often profound, but tends to be short because anesthesiologists intervene. In contrast, ward hypotension—while usually less severe—is often sustained for hours because vital signs are measured only infrequently.

A recent analysis of hypotension on surgical wards at the Cleveland Clinic identified the magnitude of the problem. Arterial pressure was continuously recorded non-invasively in postoperative patients; the continuous values were blinded to the clinical team that relied on routine nursing vital signs. Fifteen percent of patients had continuous episodes of mean arterial pressure < 70 mmHg for at least 30 min; 10% had continuous pressures < 65 mmHg for at least 15 min. Nursing records
failed to identify any hypotension at all in 70% of these patients (unpublished data).

One challenge of assessing the impact of ward hypotension on dichotomous serious outcomes such as myocardial injury or death is that these events are presumably also influenced by intraoperative events. Patients who become hypotensive during surgery are the same ones who are most likely to become hypotensive postoperatively, making it difficult to statistically isolate independent contributions. Another challenge is that ward blood pressure is usually monitored at 4–6-h intervals. The extent to which intermittent hypotension is missed, much less its duration and magnitude, is poorly characterized.

A sub-analysis of the POISE-2 trial evaluated the independent contribution of intraoperative hypotension, hypotension during the remaining day of surgery, and during subsequent hospital days. During each period, hypotension was significantly associated with the composite outcomes of myocardial infarction and death within 30 days. For example, during the remaining day after surgery, each 10 min of hypotension increased the odds 3% (95% confidence interval 1, 5%, p < 0.001). While 3% per 10 min may seem unimportant, postoperative hypotension often persists for hours, resulting in considerable cumulative insult (Fig. 4) [33].

Hypotension in intensive care units
As on surgical wards, hypotension in critical care units may be both profound and prolonged. Critical care patients are at special risk because they endure complicated and often cumulative insults. Because these patients are inherently unstable, hypotension is frequent. Hypotension in critical care patients is thus not only common but may also be especially damaging.

There is increasing evidence for an association between hypotension in critical care patients and serious complications. For example, a recent analysis of 2918 postoperative critical care patients evaluated the association between the lowest recorded mean arterial pressure and a primary composite of myocardial injury (defined by 4th-generation troponin T ≥ 0.03 ng/ml without a non-ischemic cause), and in-hospital mortality at 7 days. Mortality was included to reduce attrition bias, but nearly all events were myocardial injury. There was no significant relationship between the lowest pressure and the composite outcome at mean arterial pressures exceeding 90 mmHg. However, at lower pressures, every 10-mmHg reduction in the lowest mean pressure increased risk by about 50% [34].

Acute kidney injury is far more common than cardiac injury in critical care patients, and the severity of AKI is independently associated with in hospital mortality [35]. In the same study of 2918 postoperative critical care patients [34], there was a linear relationship between hypotension and acute kidney injury over the entire range of from 110 to 50 mmHg, with an adjusted overall hazard ratio of 1.16 per 10-mmHg reduction in the lowest recorded mean arterial pressure. When analysis was restricted to stage 2–3 injury (at least a twofold increase in creatinine), the hazard ratio increased to 1.29.

In patients with septic shock, Badin et al. showed that a mean pressure exceeding 72–82 mmHg was needed to prevent acute kidney injury [36]. Others have also concluded that a similar MAP > 73 mmHg is needed to prevent progression to kidney injury in patients with severe sepsis [37]. Both the duration and severity of hypotension matter: for example, it takes an hour of exposure to 80 mmHg to equal just a few minutes below 70 mmHg [34]. Interpretation of sepsis studies is complicated by the fact the sepsis per se causes hypotension, and worse sepsis presumably causes most hypotension and has the worst outcomes [38]. Distinguishing sepsis severity from the independent effects of hypotension is challenging, and it is likely that all such analyses suffer a degree of residual confounding.

There are clearly many causes of delirium in critical care patients [39], but hypotension may contribute. For example, patients recovering from colorectal surgery in an intensive care unit were more likely to experience delirium in the ICU if they had been hypotensive during surgery [40]. Tognoni and colleagues similarly reported that delirious patients were more likely to have had intraoperative systolic pressures < 90 mmHg [41]. Another study reported that intraoperative blood pressure variability was associated with delirium during the initial 2 critical care days, whereas relative or absolute decreases in mean arterial pressure were not [42]. Aldemir and colleagues screened 818 critical care patients daily for 10 days and reported an association between systolic pressure < 80 mmHg and delirium [43]. Delirium is difficult to assess, though, and reported differences among studies likely result at least in part from how and how often delirium was evaluated.

An association between hypotension and mortality has been reported in a mixed population, without specifically assessing the risk of myocardial injury. Dunser et al. concluded from their analysis of 274 septic patients that a MAP < 60 mmHg nearly tripled the risk of death [44]. Varpula and colleagues, in a similar but smaller cohort of septic patients, identified an association between mean pressures < 65 mmHg and 30-day mortality [45].

In most units, care of septic patients is generally guided by the Surviving Sepsis Guidelines. A strong recommendation, included in the Guidelines based on moderate-quality evidence, is to titrate vasopressors to an initial MAP target of 65 mmHg during resuscitation of septic
<table>
<thead>
<tr>
<th>Year/author</th>
<th>Clinical context</th>
<th>Single or multicenter</th>
<th>Study type</th>
<th>Patient numbers (n)</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walsh et al. [32]</td>
<td>Intraoperative non-cardiac surgery</td>
<td>Single center</td>
<td>Retrospective cohort</td>
<td>33,330</td>
<td>Risk of acute kidney injury (AKI) and myocardial injury</td>
<td>The MAP threshold where the risk for both outcomes increased was &lt; 55 mmHg. Compared with never developing a MAP &lt; 55 mmHg, those with a MAP &lt; 55 mmHg for 1–5, 6–10, 11–20, and &gt; 20 min had graded increases in their risk of the two outcomes.</td>
</tr>
<tr>
<td>Mascha et al. [23]</td>
<td>Intraoperative non-cardiac surgery</td>
<td>Single center</td>
<td>Retrospective cohort</td>
<td>104,401</td>
<td>Association of 30-day mortality and time-weighted average intraoperative mean arterial pressure (TWA-MAP) and measures of intraoperative MAP variability</td>
<td>MAP threshold of 75 mmHg represents the inflection point at which 10-min or more of sustained pressure below this threshold is associated with increased 30-day mortality. Blood pressure variability per se is only very slightly associated with postoperative mortality after non-cardiac surgery.</td>
</tr>
<tr>
<td>Monk et al. [22]</td>
<td>Intraoperative non-cardiac surgery</td>
<td>Multicenter (same database)</td>
<td>Retrospective cohort</td>
<td>18,756</td>
<td>Risk-adjusted associations between intraoperative blood pressure and 30-day mortality</td>
<td>Intraoperative hypotension, namely SBP &lt; 70 mmHg, MAP &lt; 50 mmHg, and DBP &lt; 30 mmHg, is associated with excess operative morbidity and mortality.</td>
</tr>
<tr>
<td>Sun et al. [19]</td>
<td>Intraoperative non-cardiac surgery</td>
<td>Single center</td>
<td>Retrospective cohort</td>
<td>5127</td>
<td>Association between intraoperative blood pressure and AKI during the first 2 postoperative days</td>
<td>Increased risk of postoperative AKI when intraoperative MAP was &lt; 60 mmHg for more than 20 min and &lt; 55 mmHg for &gt; 10 min.</td>
</tr>
<tr>
<td>Van Waes et al. [18]</td>
<td>Intraoperative vascular surgery</td>
<td>Multicenter</td>
<td>Prospective cohort</td>
<td>890</td>
<td>Occurrence of myocardial injury (assessed by troponin levels), myocardial infarction and 30-day mortality in relation to pre-specified intraoperative blood pressure thresholds</td>
<td>A 40% decrease from the preinduction mean arterial pressure with a cumulative duration of &gt; 30 min was associated with postoperative myocardial injury. Postoperative myocardial infarction and death within 30 days occurred more often when mean arterial pressure was &lt; 60 mmHg.</td>
</tr>
<tr>
<td>Year/author</td>
<td>Clinical context</td>
<td>Single or multicenter</td>
<td>Study type</td>
<td>Patient numbers (n)</td>
<td>Outcomes</td>
<td>Conclusions</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------</td>
<td>-----------------------</td>
<td>-----------------------</td>
<td>---------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Salmasi et al. [24]</td>
<td>Intraoperative non-cardiac</td>
<td>Single center</td>
<td>Retrospective cohort</td>
<td>53,315</td>
<td>Compare the strength of associations between absolute and relative baseline MAP as an average of all MAP readings over the last 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>surgery</td>
<td></td>
<td></td>
<td></td>
<td>(thresholds on myocardial and kidney injury)</td>
<td>MAP below absolute thresholds of 65 mmHg or relative thresholds of 20% was progressively related to both myocardial and kidney injury. Associations based on relative thresholds were no stronger than those based on absolute thresholds. Anesthetic management can thus be based on intraoperative pressures without regard to preoperative pressure.</td>
</tr>
<tr>
<td>Futier et al. [20]</td>
<td>Intraoperative non-cardiac</td>
<td>Multicenter</td>
<td>Randomized, parallel-</td>
<td>298</td>
<td>Risk of primary outcome, (composite of systemic inflammatory response syndrome and at least one organ dysfunction) by postoperative day 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>surgery</td>
<td></td>
<td>group</td>
<td></td>
<td></td>
<td>Individual tight blood pressure control reduced postoperative organ dysfunction in high-risk patients having abdominal surgery.</td>
</tr>
<tr>
<td>Abbott et al. [27]</td>
<td>Intraoperative non-cardiac</td>
<td>Multicenter</td>
<td>Retrospective cohort</td>
<td>15,109</td>
<td>Individual and dependent relationships among intraoperative heart rate, systolic blood pressure, and myocardial injury after noncardiac surgery (MINS).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prolonged heart rate &gt; 100 bpm in combination with a systolic blood pressure &lt; 100 mmHg was associated with increased risk of MINS. A combination of a lowest intraoperative heart rate &gt; 55 bpm and highest systolic pressure &gt; 160 mmHg was also associated with MINS.</td>
</tr>
<tr>
<td>Year/author</td>
<td>Clinical context</td>
<td>Single or multicenter</td>
<td>Study type</td>
<td>Patient numbers (n)</td>
<td>Outcomes</td>
<td>Conclusions</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------</td>
<td>----------------------</td>
<td>------------</td>
<td>--------------------</td>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Turan et al. (unpublished data)</td>
<td>Postoperative ward</td>
<td>Single center</td>
<td>Prospective observational</td>
<td>312</td>
<td>Evaluate the incidence and severity of hypotension, defined by MAP thresholds of 65 mmHg and 70 mmHg, during the initial 48 postoperative hours in adult patients undergoing elective abdominal surgery using continuous non-invasive blood-pressure monitoring.</td>
<td>Fifteen percent of patients had continuous episodes of mean arterial pressure &lt; 70 mmHg for at least 30 min; 10% had continuous pressures &lt; 65 mmHg for at least 15 min. Nursing records failed to identify any hypotension at all in 70% of these patients.</td>
</tr>
<tr>
<td>Sessler et al. [33]</td>
<td>Intra- and postoperative ward (including day of surgery and initial four postoperative days) non-cardiac surgery</td>
<td>Multicenter</td>
<td>Retrospective cohort</td>
<td>9765</td>
<td>Evaluated the independent contribution of intraoperative hypotension, hypotension during the remaining day of surgery, and during subsequent hospital days.</td>
<td>During each period, hypotension (defined as SBP &lt; 90 mmHg requiring treatment) was significantly and independently associated with the composite outcomes of myocardial infarction and death within 30 days.</td>
</tr>
<tr>
<td>Khanna et al. [34]</td>
<td>Postoperative surgical ICU (non-cardiac surgery)</td>
<td>Single center</td>
<td>Retrospective cohort</td>
<td>2918</td>
<td>Association between the lowest recorded mean arterial pressure and a primary composite of myocardial injury (defined by 4th-generation troponin T ≥ 0.03 ng/ml without a non-ischemic cause), and in-hospital mortality and acute kidney injury at 7 days.</td>
<td>At mean arterial pressures &lt; 90 mmHg every 10 mmHg reduction in the lowest mean pressure increased risk of myocardial injury or mortality by about 50%. Hypotension and acute kidney injury were related over a range of mean pressures from 110 to 50 mmHg.</td>
</tr>
<tr>
<td>Dunser et al. [44]</td>
<td>Multidisciplinary ICU</td>
<td>Single center</td>
<td>Retrospective cohort</td>
<td>274</td>
<td>Evaluate the association between arterial blood pressure in the first 24 h and mortality in sepsis.</td>
<td>MAP &lt; 65 mmHg nearly tripled the risk of death.</td>
</tr>
<tr>
<td>Badin et al. [36]</td>
<td>Multidisciplinary ICU</td>
<td>Multicenter</td>
<td>Prospective cohort</td>
<td>217</td>
<td>Compare the evolution of MAP during the first 24 h between patients who will show AKI 72 h after inclusion and patients who will not.</td>
<td>MAP &gt; 72–82 mmHg was needed to prevent acute kidney injury.</td>
</tr>
</tbody>
</table>
The largest trial supporting these guidelines randomized 776 patients to high (80–85 mmHg vs. low (65–70 mmHg) MAP targets in patients with vasodilatory septic shock [47]. The investigators had difficulty obtaining the targeted pressures, but did maintain good inter-group separation (85–90 mmHg vs. 70–75 mmHg). A further limitation is that clinical myocardial infarctions were observed in only nine patients, which precluded reliable assessment of this important outcome. Atrial fibrillation was more common in patients assigned to higher blood pressure, possibly consequent to greater catecholamine exposure. There was no significant overall difference in renal injury, but in a pre-planned subgroup analysis, patients with chronic hypertension who were assigned to the lower pressure target had more renal injury and more often required renal replacement therapy. Other smaller randomized trials also report that higher blood pressure targets are associated with more cardiac arrhythmias, more vasopressor use, and similar lactate, regional blood flow, and mortality compared with lower blood pressure targets [48–51].

Available data suggest that mean arterial pressures well above 65 mmHg may be needed to prevent hypotensive organ injury in postoperative critical care patients, including those who are septic. In contrast, 65 mmHg or slightly greater appears sufficient during the intraoperative period [24, 52]. The most likely explanation is that general anesthesia reduces metabolic rate about 30% [53], which presumably also reduces perfusion requirements. Furthermore, intensive care patients have coexisting insults including extreme sympathetic stimulation, fluid shifts, and often pre-existing and subsequently superimposed organ system injury. The harm threshold on surgical wards remains unknown but may well prove to be somewhere between the pressures required during surgery and those required in critically ill patients. Key perioperative and critical care hypotension studies are listed in Table 1.

**Summary and conclusions**

Mortality in the month following surgery is 1000 times greater than intraoperative mortality, and myocardial injury appears to be the leading cause. There is currently no known safe prophylaxis for postoperative myocardial injury, but there are strong associations between hypotension and myocardial injury, renal injury, and death. During surgery, the harm threshold is a mean arterial pressure of about 65 mmHg. In critical care units, the threshold however appears to be considerably greater than the currently recommended threshold of 65 mmHg. The threshold triggering injury on surgical wards remains unclear but may be in between. Much of the association between hypotension and serious complications

<table>
<thead>
<tr>
<th>Year/author</th>
<th>Clinical context</th>
<th>Study type</th>
<th>Patient numbers (n)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varpula et al. [45]</td>
<td>Medical ICU</td>
<td>Retrospective cohort</td>
<td>111</td>
<td>Identify the optimal threshold values related to outcome with special reference to continuously monitored MAP and mixed venous oxygenation</td>
</tr>
<tr>
<td>Asfar et al. [47]</td>
<td>Multidisciplinary ICU</td>
<td>Randomized control trial</td>
<td>776</td>
<td>Occurrence of 28- and 90-day mortality in the two blood pressure target groups</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year/author</th>
<th>Clinical context</th>
<th>Study type</th>
<th>Patient numbers (n)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varpula et al. [45]</td>
<td>Medical ICU</td>
<td>Retrospective cohort</td>
<td>111</td>
<td>Identify the optimal threshold values related to outcome with special reference to continuously monitored MAP and mixed venous oxygenation</td>
</tr>
<tr>
<td>Asfar et al. [47]</td>
<td>Multidisciplinary ICU</td>
<td>Randomized control trial</td>
<td>776</td>
<td>Occurrence of 28- and 90-day mortality in the two blood pressure target groups</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year/author</th>
<th>Clinical context</th>
<th>Study type</th>
<th>Patient numbers (n)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varpula et al. [45]</td>
<td>Medical ICU</td>
<td>Retrospective cohort</td>
<td>111</td>
<td>Identify the optimal threshold values related to outcome with special reference to continuously monitored MAP and mixed venous oxygenation</td>
</tr>
<tr>
<td>Asfar et al. [47]</td>
<td>Multidisciplinary ICU</td>
<td>Randomized control trial</td>
<td>776</td>
<td>Occurrence of 28- and 90-day mortality in the two blood pressure target groups</td>
</tr>
</tbody>
</table>
surely results from residual confounding, but sparse randomized data suggest that at least some harm can be prevented by intervening to limit hypotension. Reducing hypotension may improve perioperative outcomes.

Author details
1 Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Ave–P77, Cleveland, OH 44195, USA. 2 Departments of General Anesthesiology and Center for Critical Care, Anesthesiology Institute, Cleveland Clinic, Cleveland, USA.

Author contributions
Both authors contributed to manuscript drafting and approved the final manuscript.

Funding
Supported by internal funds only. Dr. Sessler consults for Edwards Lifesciences; Dr. Khanna consults for La Jolla Pharmaceuticals.

Received: 6 March 2018 Accepted: 10 May 2018
Published online: 4 June 2018

References


