Perioperative Blood Pressure Management

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Intraoperative mortality has decreased by a factor of a 100 during the last century, and deaths during surgery are now rare.[1] In contrast, mortality within the first postoperative month remains common, with about 2% of patients having inpatient noncardiac surgery dying within 30 days after surgery[2]—corresponding to more than 4 million deaths per year worldwide.[3] Postoperative deaths are most strongly associated with complications, including myocardial and acute kidney injury.[2] The risk for postoperative myocardial and acute kidney injury is largely determined by baseline factors.[4,5] But intraoperative and postoperative hypotension are also associated with myocardial and acute kidney injury, and mortality[6–12]—and differ from other risk factors in being potentially modifiable.

Hypotension during and after noncardiac surgery is multifactorial in origin, involving combinations of patient, pharmacologic, and procedural factors.[13,14] Intraoperative hypotension occurs despite frequent or even continuous intraoperative hemodynamic monitoring. Postoperative hypotension is common, profound, and prolonged—and largely missed with conventional intermittent vital sign monitoring.[15]

Avoiding perioperative hypotension is a physiologic complex challenge for anesthesiologists.[16] In this Clinical Focus Review, we summarize and discuss current evidence and open research questions regarding intraoperative and postoperative blood pressure management in patients having noncardiac surgery.

Physiology of Blood Pressure

Arterial blood pressure is the product of cardiac output and systemic vascular resistance. Blood pressure is a complex physiologic variable described clinically by systolic blood pressure, mean arterial pressure, and diastolic blood pressure. These blood pressure components result from different periods of the cardiac cycle with ventricular relaxation during diastole and contraction during systole and reflect various physiologic functions (fig. 1).

Blood pressure is regulated by multiple interrelated systems for short-term and long-term blood pressure control. The sympathetic nervous system facilitates short-term blood pressure control by local and systemic release of vasoconstrictors. In response to blood pressure changes, carotid and aortic baroreceptors transmit impulses to the autonomic nervous system to maintain normal blood pressure. Long-term blood pressure control is promoted by renal humoral control systems regulating blood volume, including the renin-angiotensin-aldosterone system. Endogenous vasopressin released from the pituitary gland increases water reabsorption from the renal tubules.

Autoregulatory mechanisms promote near-constant blood flow across various organ systems within certain blood pressure limits.[16,17] The brain and kidneys are especially protected by robust autoregulation.[17] Various factors directly or indirectly influence autoregulatory thresholds,[16,17] and the impact of vasoactive and anesthetic drugs on blood flow regulation is complex.[16]

Normal ambulatory blood pressure varies considerably among individuals,[18] and the incidence of chronic arterial hypertension increases with age.[19] Within individuals, circadian rhythms, as well as neural and hormonal changes, induce short-term fluctuations in blood pressure.[16,20] Single blood pressure measurements may therefore poorly reflect patients' blood pressure profiles.

Definitions of Perioperative Hypotension

There are no clear or widely accepted definitions of intraoperative or postoperative hypotension. Hypotension is generally defined using absolute or relative thresholds for various blood pressure components, and may specify a duration of exposure. In a systematic review, Bijker *et al.*[21] identified 140 definitions for intraoperative hypotension in 130 articles. Definitions were based on either systolic blood pressure or mean arterial pressure or a combination of both, considering either absolute thresholds or thresholds relative to a baseline.[21] The most common definition was a 20% reduction in systolic blood pressure from baseline.[21] Applying these definitions to a retrospective cohort of more than 15,000 adults who had noncardiac surgery showed that the incidence of intraoperative hypotension varies substantially depending on the selected definition.[21] For example, considering a 20% reduction in systolic blood pressure resulted in an incidence of intraoperative hypotension of 93% for a greater than or equal to 1-min exposure, 88% for a greater than or equal to 5-min exposure, and 78% for a greater than or equal to 10-min exposure.[21] Applying an absolute mean

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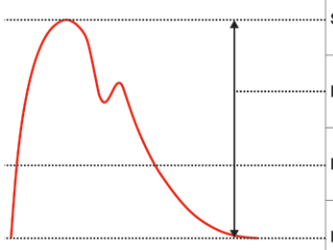

Variable	Determinants	Considerations
Systolic blood pressure	Left ventricular stroke volume, vascular compliance, and backward reflected waves	Reflects left ventricular wall tension (measure of left ventricular afterload)
Pulse pressure	Systolic blood pressure and diastolic blood pressure	Closely reflects stroke volume
Mean arterial pressure	Average pressure over the cardiac cycle	Inflow pressure for most organ systems
Diastolic blood pressure	Systemic vascular resistance	Pressure the left ventricle most overcome to begin ejecting blood into the aorta

Fig. 1. Physiology of blood pressure. Blood pressure components, their determinants, and physiologic considerations.

arterial pressure threshold of 65 mmHg yielded an incidence of 65% for a greater than or equal to 1-min exposure, 49% for a greater than or equal to 5-min exposure, and 31% for a greater than or equal to 10-min exposure.[21]

An absolute mean arterial pressure of less than 65 mmHg is frequently used to define intraoperative hypotension and is a common intervention threshold in clinical practice[22] as—on a population basis—intraoperative mean arterial pressures less than 60 to 70 mmHg are associated with myocardial injury,[6,7] acute kidney injury,[6–8] and death[10–12] in adults having noncardiac surgery. However, there surely is not a single blood pressure threshold that defines perioperative hypotension in all patients because baseline blood pressure values[18] and lower limits of autoregulation[23] vary considerably among individuals.

Harm from hypotension appears to mostly accrue from brief periods at low pressures rather than from prolonged exposure to moderate pressures. Consequently, measures that characterize hypotensive excursions are generally more helpful than case averages. Perioperative hypotension can be defined as a binary event based on a single blood pressure value (*e.g.*, mean arterial pressure less than 65 mmHg at least once) or by cumulative or consecutive time with blood pressure under a certain threshold (*e.g.*, mean arterial pressure less than 65 mmHg for at least 5 consecutive or cumulative minutes). However, dichotomous definitions (such as hypotensive or not) discard much information and therefore poorly characterize continuous measures. More sophisticated definitions consider exposure time, such as cumulative minutes of mean arterial pressure less than 65 mmHg. Even better ones consider both duration and severity of exposure such as area under a threshold, which has units of mmHg times minute. A similar alternative is time-weighted average blood pressure under a threshold, which is area divided by duration, thus having units of mmHg.[24] The distinction is that time-weighted average under a threshold is normalized for time, whereas area under a threshold is naturally larger during longer procedures.

Blood Pressure Monitoring

There are three common blood pressure measurement approaches[25]: (1) intermittent oscillometric; (2) continuous intraarterial; and (3) continuous noninvasive using a finger cuff (*i.e.*, volume clamp method).

Intermittent automated oscillometric measurements using an inflatable, occluding cuff is the most frequently used blood pressure measurement approach. However, oscillometric monitors provide blood pressure values only intermittently (they are usually set to measure at 3- to 5-min intervals). The measurement performance of oscillometric methods depends on the selection of the appropriate cuff size relative to the circumference of the relevant extremity. Additionally, oscillometric monitors use different proprietary algorithms to assess blood pressure from cuff oscillations, and the agreement between oscillometric and intraarterial blood pressure measurements is highly variable.[26] Oscillometric methods exhibit poor measurement performance at blood pressure extremes. Specifically, oscillometric methods overestimate low and underestimate high blood pressures, thus potentially missing both hypotension and hypertension.[27,28]

Direct continuous intraarterial blood pressure measurement using an arterial catheter remains the clinical reference method. Major complications after radial, brachial, and femoral artery cannulation such as ischemia, major bleeding, or severe infections are rare.[29–31] Radial systolic blood pressure may overestimate central systolic blood pressure due to pulse pressure amplification during propagation of the pulse wave from the heart to the periphery.[32] However, radial blood pressure underestimates central blood pressure in septic patients treated with vasopressors,[33,34] patients having liver transplant surgery,[35] and cardiac surgery patients after cardiopulmonary bypass.[36,37] Invasive blood pressure monitoring is only reliable when the pressure transducer is correctly leveled and zeroed, when the recorded blood pressure waveform is free of artifacts, and when the

dynamic response of the catheter/tubing/transducer system (*i.e.*, "damping") is adequate.[38] Continuous invasive blood pressure monitoring detects twice as many hypotensive minutes, and triggers a third more vasopressor boluses than intermittent oscillometric blood pressure measurements in patients having major noncardiac surgery.[39]

Noninvasive finger cuff methods using the volume clamp method (also called vascular unloading technology) allow continuous blood pressure monitoring without arterial cannulation.[25] These systems use finger cuffs housing an infrared photodiode and light detector to plethysmographically estimate the blood volume in the finger arteries as it changes during the cardiac cycle. The system controls finger cuff pressure to keep blood volume in the finger arteries constant. The arterial blood pressure waveform is then reconstructed from the cuff pressure needed to keep blood volume in the finger arteries constant.[25] Because pulsatile blood flow in the finger is a prerequisite for finger cuff pressure assessment, the method is unreliable during circulatory shock or high-dose vasopressor therapy.

Finger cuff devices from various manufacturers use different methods to account for changes in vascular tone, to obtain the finger blood pressure signal, and to estimate brachial blood pressure from finger blood pressure (either by using proprietary scaling algorithms or by calibrating finger blood pressure to oscillometric upper-arm cuff blood pressure measurements).[25,40] Thus each device needs to be validated separately against reference methods. Validation studies comparing continuous finger cuff blood pressure measurements to arterial catheter–derived measurements show heterogeneous results, but several studies demonstrated interchangeability between blood pressure measurements obtained by either method.[41] In pilot randomized trials, continuous noninvasive finger cuff blood pressure monitoring reduced intraoperative hypotension compared to intermittent oscillometric blood pressure monitoring.[24,42]

Other blood pressure monitoring methods—such as the hydraulic coupling method,[43] applanation tonometry,[44] the pulse wave transit time method,[45] or the pulse decomposition method[46]—may prove to be important alternatives to conventional perioperative blood pressure monitoring methods, but all have inherent technical limitations and need meticulous validation before being broadly adopted in routine care.[47,48]

Anesthesia professionals routinely evaluate blood pressure changes and try to predict when patients will become hypotensive. A recent advance is using machine learning, which is a subset of artificial intelligence, to analyze features of the blood pressure waveform to predict hypotension. Hatib *et al.*[49] proposed a machine learning algorithm that predicts hypotension, defined as mean arterial pressure less than 65 mmHg for at least 1 min, 5 or more min in advance—thus giving clinicians an opportunity to intervene and perhaps prevent hypotension.[49,50] This "hypotension prediction index" indicates the probability of impending hypotension as a unitless number ranging from 0 to 100. The final prediction model is based on 51 features of the arterial blood pressure waveform that were selected from more than 3,000 individual and more than 2.6 million combinatorial waveform features.[49] The algorithm was trained on blood pressure waveforms of 1,334 surgical or critically ill patients and externally validated in 204 patients having surgery, showing a sensitivity of 88% and a specificity of 87% to predict hypotension 15 min before the event.[49] In another validation study in 255 patients having major surgery, the hypotension prediction index predicted intraoperative hypotension up to 15 min before the event with a sensitivity and specificity of 81% each.[51] Naturally, the hypotension prediction index algorithm cannot predict hypotension consequent to clinical interventions, including hypotension caused by pressure on major vessels by surgeons or changes in patient position such as reverse Trendelenburg position. In a single-center trial in patients having hip arthroplasty, intraoperative hypotension occurred less frequently and for shorter durations in 25 patients randomized to hypotension prediction index–guided blood pressure management compared to 24 patients with routine blood pressure management and 50 patients from a historic control group.[52] In another small preliminary single-center trial in 68 noncardiac surgery patients, hypotension prediction index–guided blood pressure management markedly reduced the time-weighted average of a mean arterial pressure less than 65 mmHg, as well as the incidence and absolute and relative duration of hypotension compared with routine care.[53] However, in another trial of 214 patients having moderate- to high-risk inpatient noncardiac surgery, no reduction in the amount of hypotension was observed in patients randomized to management with hypotension prediction index-guided hemodynamic and fluid management.[54]

Perioperative Blood Pressure and Postoperative Outcomes

Acute kidney injury and myocardial injury are major postoperative outcomes associated with hypotension in adults having noncardiac surgery. Many studies define postoperative acute kidney injury based on the Kidney Disease: Improving Global Outcomes (KDIGO) definition that defines acute kidney injury as any of the following criteria: increase in serum creatinine by greater than or equal to 0.3 mg/dl within 48 h, increase in serum creatinine greater than or equal to 1.5 times the baseline value (which is known or presumed to have occurred within the previous 7 days), or urine volume less than 0.5 ml · kg^{-1} · h^{-1} for 6 h.[55] Many studies on postoperative acute kidney injury exclude the oliguria criteria of the KDIGO definition. Additionally, many studies only consider the first 48 h after surgery when using the greater than or equal to 0.3 mg/dl serum creatinine increase criterion, although the KDIGO definition refers to a greater than or equal to 0.3 mg/dl

serum creatinine increase within any 48-h window within the observation period.[56]

Myocardial infarction is defined by fourth Universal Definition of Myocardial Infarction.[57] However, it is now known that more than 90% of postoperative myocardial injury is asymptomatic, and that most injury is not accompanied by clinical signs such as electrocardiogram changes that are required for diagnosis of myocardial infarction.[58–60] Troponin elevation of apparently ischemic origin, with or without symptoms and signs, is therefore termed "myocardial injury after noncardiac surgery."[61] Although most myocardial injury patients have underlying coronary artery disease, the etiology of myocardial injury after noncardiac surgery seems to predominantly result from oxygen supply–demand mismatch rather than thrombosis.[61,62] Myocardial injury after noncardiac surgery is common, with a reported incidence ranging from 8 to 18% in surgical inpatients depending on baseline and operative risk,[2,58–60] and is associated with postoperative nonfatal cardiac arrest, congestive heart failure, stroke, and 30-day mortality.[2,58–60] Mortality in patients with myocardial injury after noncardiac surgery is 4 to 10%.[56–58] Mortality after myocardial injury not fulfilling the additional criteria required for a diagnosis of myocardial infarction is nearly as high as after myocardial infarction.[59,60]

Baseline patient risk factors such as age and cardiovascular history are far more strongly associated with postoperative acute kidney injury[4,5] and myocardial injury[5] than intraoperative hypotension. But hypotension, in contrast to most baseline risk factors, is potentially modifiable—and therefore of special interest.

Intraoperative Blood Pressure

Various registry analyses have identified population harm thresholds for intraoperative hypotension by exploring associations between blood pressure and postoperative outcomes in patients who had noncardiac surgery with general anesthesia.[22,63]

Cumulative evidence suggests that on a population basis, intraoperative mean arterial pressures less than 60 to 70 mmHg are associated with myocardial injury,[6,7] acute kidney injury,[6–8] and death[10–12] in adults having noncardiac surgery. The association between organ injury and hypotension is a function of both severity and duration, with lower pressures requiring shorter exposures.[6,7,63] A systematic review of 42 studies summarized reported risks of myocardial injury, acute kidney injury, and death depending on the severity and duration of intraoperative hypotension.[63] The risk of any end-organ injury was slightly increased when mean arterial pressures were sustained at less than 70 mmHg for just 10 min.[63] The risk was moderately increased with exposures to mean arterial pressures less than 65 to 60 mmHg for at least 5 min, or any exposure to mean arterial pressures less than 55 to 50 mmHg.[63] High risk of any end-organ injury was reported for exposures to mean arterial pressures less than 65 mmHg for at least 20 min, mean arterial pressures less than 50 mmHg for at least 5 min, or any exposure to mean arterial pressures less than 40 mmHg.[63]

Over a wide range of preoperative baseline blood pressures, the association between intraoperative hypotension and postoperative myocardial injury is comparably strong when intraoperative hypotension is defined by absolute or relative mean arterial pressure thresholds.[7] For example, an absolute mean arterial pressure threshold of 65 mmHg and a relative reduction from clinic baseline pressure of 30% are comparably predictive for myocardial injury (fig. 2).[7] However, absolute thresholds are easier to use than relative thresholds. Immediate preinduction blood pressures poorly reflect ambulatory blood pressures,[18] which are considered the best characterization of baseline blood pressure.[16,64]

Systolic blood pressure and mean arterial pressure are roughly comparably associated with postoperative acute kidney and myocardial injury, but of course at different harm thresholds. For systolic blood pressure, harm begins to accrue below about 90 mmHg, whereas the threshold is about 65 mmHg for mean arterial pressure.[5] Blood pressure variability is only marginally associated with postoperative mortality.[10]

Clinically important hypotension occurs not only during surgery but also between anesthetic induction and incision.[65] Although the preincision period is short compared to the entire intraoperative duration, in one study it accounted for a third of all hypotension observed throughout the entire anesthetic and was independently associated with major complications.[66] Hypotension occurring before surgical incision is presumably largely determined by baseline patient risk factors and anesthetic management. A corollary is that blood pressure during anesthesia induction is at least mostly under control of anesthesiologists.

Postoperative Blood Pressure

Postoperative hypotension during the initial days after surgery is common[9] and is independently associated with postoperative myocardial injury[67] and a composite of myocardial infarction and death,[9] even after adjusting for intraoperative hypotension. Interestingly, in one cohort of patients having intermediate- to high-risk noncardiac surgery, only postoperative hypotension—and not intraoperative hypotension—was associated with myocardial injury.[67] In patients admitted to the intensive care unit after noncardiac surgery, postoperative hypotension is associated with acute kidney injury and a composite of myocardial injury and death.[68]

Postoperative hypotension may thus be a potentially modifiable risk factor for organ injury. The relation between intraoperative and postoperative blood pressures requires further investigation as the incidence and severity of intraoperative hypotension may help identify patients at risk for postoperative hypotension.

While frequent blood pressure assessment is routine in operating rooms and intensive care units, postoperative

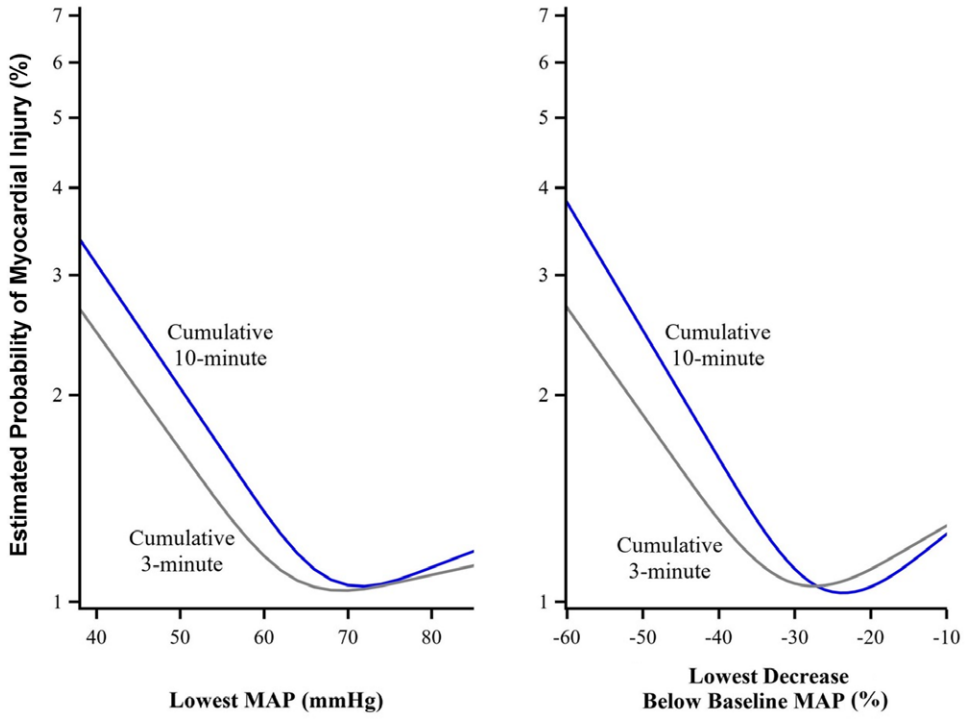

Fig. 2. Lowest mean arterial pressure (MAP) thresholds for myocardial injury after noncardiac surgery. The *left-hand graph* shows multivariable relationships between myocardial injury after noncardiac surgery and lowest absolute MAP thresholds that were sustained for a cumulative 3 and 10 min. The *right-hand graph* shows multivariable relationships between myocardial injury after noncardiac surgery and lowest relative MAP thresholds compared with preoperative clinic MAP that were sustained for a cumulative 3 and 10 min. Multivariable logistic regressions were smoothed by restricted cubic spline with 3 degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. With permission from Salmasi *et al.*[7]

blood pressure monitoring remains sparse on general care wards. For example, vital sign assessments at 4-h intervals miss most postoperative hypotension, even when it is profound and prolonged (fig. 3).[15] Presumably, even more hypotension is missed when vital signs are recorded at yet longer intervals. Untethered continuous ward vital sign monitors are now available and should be considered when practical.[69]

Therapeutic Approaches to Perioperative Hypotension

Perioperative hypotension is associated with adverse postoperative outcomes, although there is currently little evidence that the relationship is causal or amenable to intervention. Even assuming that the associations between hypotension and organ injury are causal, it remains unclear which blood pressures should be targeted in individual patients during and after noncardiac surgery.[22] On a population basis, harm thresholds for organ injury appear to be about 60 to 70 mmHg for mean arterial pressure and 90 to 100 mmHg for systolic blood pressure.[22] However, some patients presumably require higher intraoperative blood pressures to prevent injury. Postoperatively, harm thresholds remain largely unknown, but are presumably higher than during surgery because metabolic rate is higher.[70]

Defining perioperative blood pressure intervention thresholds for individual patients is challenging because blood pressure regulation depends on complex autoregulatory mechanisms and normal blood pressure varies considerably among individuals.[18] In patients with chronic arterial hypertension, blood flow autoregulation curves are shifted to the right, toward higher blood pressures. Therefore, patients with chronic arterial hypertension possibly tolerate less hypotension than normotensive patients and may need higher perioperative blood pressures.[12]

One multicenter randomized trial tested the hypothesis that individualizing blood pressure targets reduces a composite primary outcome of systemic inflammatory response syndrome and organ dysfunction of at least one major organ system compared to routine care in 292 patients having major surgery.[71] Patients assigned to individualized management were given norepinephrine continuously during surgery to achieve systolic blood pressures within 10% of the preoperative resting value. Patients in the routine management group

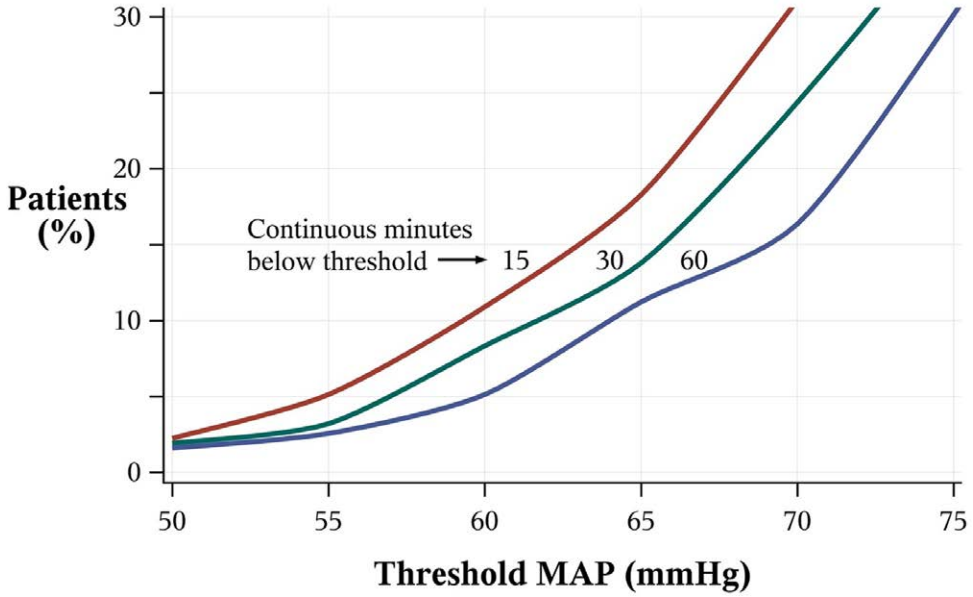

Fig. 3. Postoperative hypotension. Blood pressure was recorded at 1-min intervals during the initial 48 h in adults recovering from abdominal surgery using a noninvasive monitoring system. The figure shows continuous hypotensive episodes of various durations under various thresholds. For each patient, the total time of the observed longest continuous hypotensive episode with mean arterial blood pressure (MAP) readings below various thresholds was computed. The percent of patients with at least that many minutes below the threshold is plotted. For example, the *green line* shows that 24% of patients had a continuous episode of MAP less than 70 mmHg lasting at least 30 min. Only about half of these episodes were identified by routine vital sign assessments at 4-h intervals. With permission from Turan *et al.*[15]

were given ephedrine boluses when their systolic blood pressure was less than 80 mmHg or more than 40% lower than preoperative values. The primary outcome occurred in 38% of patients assigned to individualized and 52% of patients assigned to routine blood pressure management (absolute risk difference, −14%; 95% CI, −25 to −2%). This trial thus provides evidence that individualizing blood pressure targets may reduce postoperative organ dysfunction compared to routine care in patients having major surgery.[71]

Further studies are needed to confirm that individualizing blood pressure intervention thresholds improves patient outcome. Using individualized thresholds requires identifying how to reliably determine preoperative baseline blood pressure. It may be determined by repeated standardized measurements in the hospital or by ambulatory blood pressure monitoring. Ambulatory blood pressures presumably best reflect the patients' normal blood pressure.[16,18,64] However, the optimal timing, setting, and technique for ambulatory blood pressure monitoring remain unclear.[16,64,72]

The ultimate goal of perioperative blood pressure management is providing adequate organ perfusion. Organ perfusion pressure is the difference between inflow and outflow pressures. Mean arterial pressure is the inflow pressure for most organ systems, while the outflow pressure is the higher of either central venous pressure or specific surrounding organ pressure (*e.g.*, intracranial, intraabdominal, intrathoracic pressure). Therefore, mean arterial pressure is a clinically available surrogate of perfusion pressure, but needs to be considered in light of organ-specific outflow pressures.

Additionally, the type of surgery, together with various surgery-related events (*e.g.*, changes in position, clamping of arteries, bleeding), all contribute to defining the optimal blood pressure for an individual patient at any given time. For instance, in patients having surgery in the beach chair position, hydrostatic pressure differences between the level of the heart and the level of the brain should be considered.

Since perioperative hypotension has multiple causes, treatment should focus on underlying causative mechanisms to the extent that they can be identified. This may include reducing the dose of vasodilating anesthetics, treating vasodilation with vasopressors, increasing blood flow with inotropes, increasing heart rate with atropine, or treating intravascular hypovolemia with crystalloids, colloids, or blood products. At this point, it remains quite unclear which vasopressors and type of fluids best treat perioperative hypotension. Nonpharmacologic treatments for perioperative hypotension include peristaltic pneumatic compression of the legs[73] and Trendelenburg positioning.

The choice of therapeutic interventions remains subject to ongoing debate since it remains unclear which (if any) antihypotensive treatments substantially improve outcomes, and how therapeutic interventions influence autoregulatory mechanism and microcirculatory function.[22]

Future Research

Perhaps the most important remaining research question is whether there is a causal relationship between intraoperative and/or postoperative blood pressures and organ injury. The relationship between hypotension and serious complications is currently supported by many observational analyses, but only by sparse randomized data.[71] Thus, robust randomized trials testing the hypothesis that avoiding intraoperative and postoperative hypotension improves postoperative outcomes are needed. Similarly, which blood pressure intervention thresholds should be used intraoperatively and postoperatively remains to be determined, as well as whether they should be defined by absolute thresholds or relative blood pressure changes.

Trials are needed to determine the best treatment strategy for intraoperative and postoperative hypotension. Presumably, interventions targeting various causes of intraoperative and postoperative hypotension are preferable to pragmatic approaches such as simply giving vasopressors. And finally, trials are needed to evaluate potential benefits from current and future monitoring technologies, as well as treatment recommendations based on machine learning and artificial intelligence.

Conclusions

Hypotension is common during noncardiac surgery, and is associated with myocardial injury,[6,7] acute kidney injury,[6–8] and death.[10–12] Postoperative hypotension is common, often prolonged, and associated with myocardial injury and death.[9,67] Postoperative hypotension on general care wards is largely missed by conventional intermittent blood pressure monitoring.[15]

Evidence from registry analyses suggests that the intraoperative population harm thresholds for organ injury are 60 to 70 mmHg for mean arterial pressure and 90 to 100 mmHg for systolic blood pressure.[22] Postoperative harm thresholds remain unclear, but are probably slightly higher.

Serious cardiovascular[5] and renal complications[4,5] are more strongly associated with baseline risk than hypotension, but hypotension differs from other risk factors in being potentially modifiable. The question, then, is whether observed associations between hypotension and complications are causal, and thus amenable to intervention. There is currently only sparse evidence from trials to establish a causal connection and identify treatment effects. For that matter, when and how best to intervene also remains unknown.

Pressing research needs include determining whether preventing and treating hypotension reduces complications, and to what extent. If the relationship is indeed causal, the next steps will be to determine when intervention is helpful, and which interventions are safe and effective.

In the meantime, clinicians should consider hypotension to be a modifiable risk factor that is associated with renal and myocardial injury, as well as death. Pending results from robust clinical trials, avoiding hypotension seems prudent. Based on current evidence and pathophysiologic rationale, we suggest that mean arterial pressure should be kept above 65 mmHg during surgery and somewhat higher postoperatively.

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Competing Interests

Dr. Saugel received honoraria for consulting and giving lectures, and refunds of travel expenses from Edwards Lifesciences Inc. (Irvine, California); honoraria for consulting and giving lectures, institutional restricted research grants, and refunds of travel expenses from Pulsion Medical Systems SE (Feldkirchen, Germany); institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from CNSystems Medizintechnik GmbH (Graz, Austria); institutional restricted research grants from Retia Medical LLC (Valhalla, New York); honoraria for giving lectures from Philips Medizin Systeme Böblingen GmbH (Böblingen, Germany); and honoraria for consulting, institutional restricted research grants, and refunds of travel expenses from Tensys Medical Inc. (San Diego, California). Dr. Sessler is a consultant for Edwards Lifesciences (Irvine, California), Pacira Biosciences (Parsippany, New Jersey), and Sensifree (Cupertino, California).

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

A "Soothing" Syrup? How "Father" Wiley Saved Infants from "Mother" Winslow's Morphine Elixir

From the early nineteenth to the early twentieth century, Mrs. Winslow's Soothing Syrup (*top*) was marketed in the United States as a panacea for ailments that plagued infants: teething, diarrhea, colic, etc. To ensure happy or sleeping children like those depicted above (*lower left*), Charlotte "Mother" Winslow and her legacy firms spiked her Soothing Syrup with morphine and alcohol. Over the course of a century, sales of millions of bottles worldwide caused thousands of infant deaths. Fortunately, Dr. Harvey Washington Wiley (*lower right*), Chief Chemist at the U.S. Department of Agriculture and future "Father of the Food and Drug Administration," intervened by facilitating passage of the Pure Food and Drug Act (1906). Several amendments further limited the sale of opioids, leading to the removal of morphine from a syrup that was more sinister than soothing. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology, Schaumburg, Illinois.)

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