

# Personalizing the Definition of Hypotension to Protect the Brain

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Originally championed by Harvey Cushing in the early 1900s, the measurement of blood pressure during anesthesia and surgery became widespread in the 1920s.<sup>1,2</sup> Physicians soon recognized the relationship between intraoperative hypotension and adverse patient outcomes.<sup>3</sup> Nonetheless, over a century later there is presently no agreement on a universally accepted definition of hypotension.<sup>4</sup> In this focused review, we will briefly discuss a common approach for defining hypotension based on arbitrary or population-driven thresholds. We then will propose a novel method for potentially defining hypotension individually based on monitoring cerebral blood flow autoregulation.

## Current Approach for Determining Hypotension Threshold

The controversy regarding how to best define intraoperative hypotension was highlighted in a systematic review by Bijker *et al.*,<sup>4</sup> who identified 130 manuscripts that utilized 140 different definitions for this term. The most frequently used definition (12.9% of articles) was a relative decrease in systolic blood pressure more than 20% from baseline followed by the combination of systolic blood pressure of less than 100 mmHg or a more than 30% decrease from baseline (7.9% of articles). These definitions, however, were mostly based on opinion and historical precedent. Further, determining a true “baseline” blood pressure is challenging in an operative setting.

Another approach for defining hypotension is to determine blood pressure cutoffs associated with adverse perioperative outcomes. In this regard, Wesselink *et al.*<sup>5</sup> performed a systematic review of 42 high-quality publications to synthesize blood pressure cutoffs for defining hypotension based on the relationship with adverse patient outcomes after noncardiac surgery. Thresholds of intraoperative mean arterial pressures (MAPs) in relation to any adverse events were synthesized into incremental risk categories (table 1). The risk for organ injury (*e.g.*, acute kidney injury, myocardial infarction, stroke, or delirium) or mortality increased progressively depending on the degree and duration of MAP decrements from baseline starting at a MAP of less than 80 mmHg. Generalizing these results to every day

practice, though, is tempered by the varying frequency of cardiovascular disease and other risk factors in any given patient. The applicability of these data to women, minority patients, and the aged whom were under represented in these studies is further unclear. Moreover, hypotension can be a proximate cause of organ injury or it can exacerbate injury from other sources such as embolism (*i.e.*, thrombotic or atheromatous embolism). Finally, the potential benefits of prospectively maintaining blood pressure above these cutoffs for the prevention of perioperative complications particularly brain injury is not clear.

Although the focus of the systematic review by Wesselink *et al.*<sup>5</sup> was noncardiac surgery, there are data showing a relationship between low MAP during cardiac surgery using cardiopulmonary bypass (CPB) and adverse patient outcomes including stroke and acute kidney injury.<sup>6–9</sup> Blood pressure during CPB is typically maintained at a level determined in part by institutional practices that limit the extreme fluctuations necessary to determine the minimal tolerable MAP. Randomized studies testing the benefits of “low” versus “high” MAP targets during CPB on patient outcomes have produced conflicting findings and do not provide guidance on the lowest tolerable blood pressure for a given patient during surgery.<sup>9–13</sup> Defining various MAP cutoffs for causing organ injury must acknowledge that complications from surgery result from a combination of patient- and procedure-related factors that may or may not necessarily include compromised organ perfusion. Moreover, the assumption that a single threshold for hypotension applies to all patients is unsubstantiated. Finally, the safety of simply maintaining a MAP of more than 80 mmHg in all patients in all clinical situations is not specifically addressed in these studies.

## Hypotension Defined Based on Cerebral Blood Flow Autoregulation

Several homeostatic processes contribute to the adequate delivery of oxygen- and nutrient-rich arterial blood to the brain to match metabolic demand as reviewed elsewhere.<sup>14</sup> These processes operate at distinct frequencies to precisely regulate cerebral blood flow. At the same time, cerebral microcirculatory flow is influenced by metabolically

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**Table 1.** Relationship between Blood Pressure Cutoffs and Adverse Patient Outcomes

Mildly elevated risk (odds ratio, 1.0 to 1.4)
MAP < 80 mmHg for ≥ 10 min
MAP < 70 mmHg < 10 min
Moderate risk (odds ratio, 1.4 to 2.0)
MAP < 60 to 65 mmHg for > 5 min
MAP < 50 mmHg for any duration
High risk (odds ratio > 2.0)
MAP < 65 mmHg for ≥ 20 min
MAP < 50 mmHg for ≥ 5 min
Any exposure to MAP < 40 mmHg

Summary of meta-analysis results from 42 studies evaluating the relationship between blood pressure cutoffs and adverse patient outcomes including mortality after noncardiac surgery.<sup>5</sup> Categories of elevated risk are based on the strength of a given mean arterial pressure (MAP) threshold and organ injury and/or death.

driven neurovascular coupling, oxygen and carbon dioxide levels, and glucose concentrations. Pressure autoregulation of cerebral blood flow is an additional homeostatic process that maintains a steady blood supply to the metabolically demanding brain. When blood pressure is below or above the limits of autoregulation, cerebral blood flow becomes pressure-passive or directly dependent on blood pressure. There is a long-standing belief that the lower limit of cerebral blood flow autoregulation is 50 mmHg and the upper limit of autoregulation 150 mmHg based on the seminal report by Lassen in 1959.<sup>15</sup> The acceptance of these limits of autoregulation as a guiding principle for perioperative hemodynamic management was challenged over two decades ago by Drummond,<sup>16</sup> who highlighted both the paucity of data to support this assumption and the simplicity of the statistical analysis used for its derivation.

Contemporary digital processing methods now make it possible to monitor cerebral blood flow autoregulation at the bedside. Work by our group in patients undergoing cardiac and noncardiac surgery using these methods have found in fact that the lower limit of autoregulation in anesthetized patients varies markedly between 40 and 90 mmHg for adults and 30 to 55 mmHg for pediatric patients, confirming earlier observations.<sup>17–19</sup> We reported that there is no relationship between the lower limit of autoregulation during anesthesia and awake MAP, systolic blood pressure, age, or medical history.<sup>18,19</sup> Together, the data support the notion that the definition of hypotension is an individual definition and cannot be accurately determined based on population data.

Different vascular beds respond differently to hemodynamic challenges. For instance, in a piglet hemorrhagic shock model, renal autoregulation and cerebral autoregulation can be demonstrated at baseline, but early in the process of hemorrhage, renal blood flow is reduced, and the kidney becomes pressure-passive even at arterial blood pressures previously linked to normal renal blood flow and autoregulation.<sup>20</sup> That is, kidney perfusion is not only

dependent on blood pressure but also cardiac output. In that study, renal blood flow was 75%, 50%, and 25% of baseline when MAP was 60, 45, and 40 mmHg, respectively. The brain did not reach these decrements in flow until MAPs of 30, 25, and 15 mmHg. The brain continues to receive normal blood flow, demonstrating intact cerebral blood flow autoregulation until the point where shock results in a further fall in blood pressure below the lower limit of autoregulation whereby cerebral blood flow decreases. Thus, ensuring a blood pressure suitable for brain perfusion may not necessarily ensure renal or other splanchnic organs that are further dependent on cardiac output. However, there are currently no widely accepted patient bedside monitoring for these organs. Further, identifying patients with a higher MAP threshold of autoregulation who may require higher than normally accepted blood pressure may more likely result in more optimized renal perfusion than a lower blood pressure.

The effect of cardiac output on cerebral blood flow has been recently reviewed.<sup>21</sup> A compilation of data from nonanesthetized individuals demonstrates that cerebral blood flow is correlated with cardiac output *via* different mechanisms. Pressure autoregulation, however, likely remains functional despite shifting up or down of the cerebral blood flow–blood pressure relationship. In contrast, data derived from animals and humans during CPB have shown that blood pressure above a critical threshold (presumably the lower limit of autoregulation) is the main determinant of adequate cerebral blood flow, not systemic flow rate (equivalent of cardiac output).<sup>22,23</sup> Notably, during CPB, flow can be manipulated without the administration of vasoactive drugs that may indirectly influence cerebral blood flow.

Pressure autoregulation is often maintained despite perturbations in other parameters that can influence cerebral blood flow. In an animal experiment, for example, we have shown that hypercarbia (without acidosis or increased intracranial pressure [ICP]) can impair autoregulation, but if there is a sufficient increase in blood pressure, autoregulation is restored.<sup>24</sup> In that experiment, the lower limit of autoregulation in piglets with a PaCO<sub>2</sub> of more than 80 mmHg was 75 mmHg (95% CI, 73 to 77 mmHg) compared with normocarbic controls where the lower limit of autoregulation was 45 mmHg (95% CI, 43 to 47 mmHg). The lower limit of autoregulation was correlated with PaCO<sub>2</sub> levels (spearman correlation = 0.8243, *P* < 0.0001).

Current arbitrary definitions of hypotension originate in part from data obtained 40 to 65 yr ago that opined that the lower limit of autoregulation for a nonanesthetized patient was equal to a 25% decrease in MAP from baseline.<sup>16,25</sup> Interestingly, in the paper describing cerebral blood flow autoregulation, Lassen included the term “hypotension” on the *x* axis of the graph starting at 70 mmHg.<sup>15</sup> Organ blood flow can be compromised, however, by arterial vascular disease, especially atherosclerosis. Regional myocardial

blood flow, for example, can be reduced below an ischemic threshold in the presence of a restrictive coronary artery stenosis at a blood pressure (diastolic blood pressure) that is adequate for other organs. Thus, we cannot expect a neuro-monitor to elucidate arterial blood pressure thresholds that satisfy all organ beds. However, clinicians can only choose one blood pressure goal in the operating room and the intensive care unit (ICU), and protecting the brain is of paramount importance.

### Monitoring Cerebral Blood Flow Autoregulation

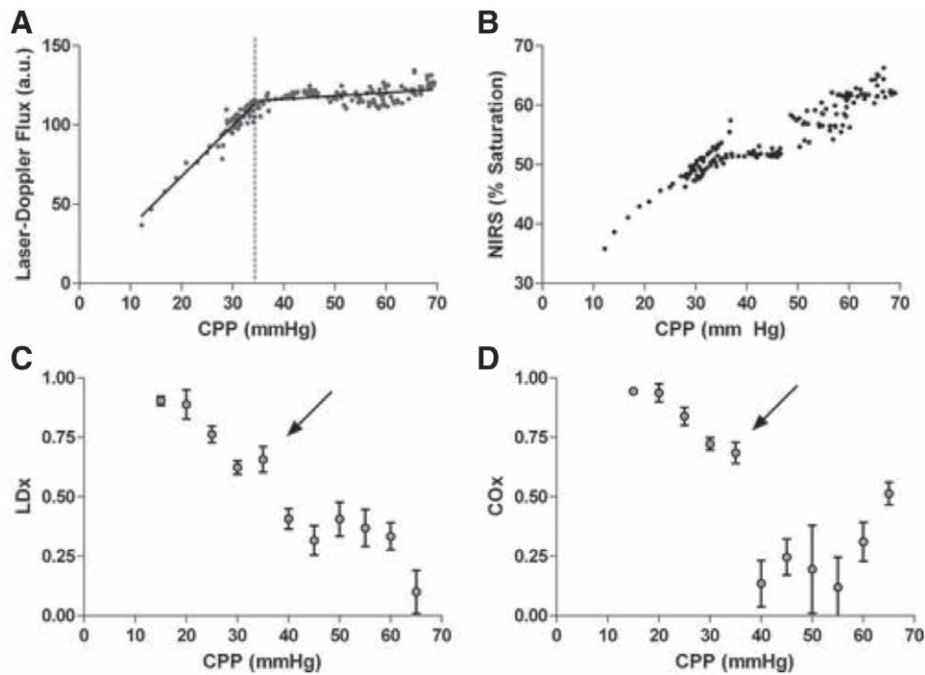
Autoregulation can be monitored continuously using a variety of methods that have been inconsistently validated using animal models and clinical outcome studies. However, many methods that have been asserted to measure autoregulation have not been demonstrated to do so.<sup>26</sup> Most methods require a continuous measure of arterial blood pressure with a continuous measure of brain-blood flow, blood volume, or oxygenation. These methods pair the blood pressure waveform as input with the synchronous brain measure waveform as output in a mathematical model, placing autoregulation as a filter between the two signals.

A classic example of this type of autoregulation monitoring is the mean velocity index, which pairs arterial blood pressure as an input and transcranial Doppler measured cerebral blood flow velocity as the output signal.<sup>27</sup> The autoregulation filtering function of the cerebral vasculature is then modeled as a Pearson's correlation coefficient between the two signals focusing on low frequency changes (*i.e.*, 0.004 to 0.04 Hz) associated with autoregulatory vasomotor adaptations. When blood pressure is below the lower limit of autoregulation or above the upper limit of autoregulation, autoregulation is dysfunctional or there is no filter between the input and output signals. The result is that the cerebral blood flow velocity is correlated with blood pressure. When autoregulation is intact, there is an active filter demonstrated between the input and output signals, which results in no correlation between measures of cerebral blood flow and blood pressure.

Another commonly used example of an autoregulation monitor pairs arterial blood pressure with ICP.<sup>28</sup> In this example, termed the pressure reactivity index, the ICP serves as a surrogate measure of cerebral blood volume. That is, vasodilation or vasoconstriction in response to changes in blood pressure collectively increases or decreases cerebral blood volume, respectively. The pressure reactivity index is simply the Pearson's correlation coefficient between low frequency changes in ICP and cerebral perfusion pressure to model the filtering function of vascular reactivity. During a state of impaired vascular reactivity, the ICP is unfiltered as an output signal from the arterial blood pressure, resulting in positive correlation between the two. When autoregulation is intact, the ICP is altered relative to the arterial blood pressure, and no correlation is seen.

Variations of autoregulation monitoring have used a variety of intracranial hemodynamic measurements, including near-infrared spectroscopy-based measures, brain tissue oxygen, ultrasonic time-of-flight measures, and other surrogate measures of cerebral blood flow, blood volume, or oxygenation. Animal models have been used to create static autoregulation curves delineating a gold standard lower limit of autoregulation and then testing various autoregulation monitors above and below this standard with receiver operator characteristics.<sup>29,30</sup> Using this method we have validated near-infrared spectroscopy-based cerebral oximetry index in animals against laser Doppler flux measurement of cerebral blood flow (fig. 1) and in humans under anesthesia against transcranial Doppler cerebral blood flow velocity.<sup>29</sup> Few published methods have been validated in this way.<sup>30-32</sup> This technique involves processing digital regional cerebral oxygen saturation signals from a commercially available near-infrared spectroscopy monitor along with arterial blood pressure signals from a standard hemodynamic monitor. The signals are then time-integrated and filtered to focus on low frequencies (less than 0.05 Hz) associated with autoregulation mediating vaso-reactivity. This filtering eliminates high-frequency noise from respiratory or pulse frequencies and hemodilution as occurs with CPB. Next, a continuous, moving Pearson's correlation coefficient was calculated between MAP and laser Doppler flux or regional cerebral oxygen saturation signals, generating the variable laser Doppler index and cerebral oximetry index using 10-s average values from a 300-s duration window. Average values of laser Doppler index and cerebral oximetry index are placed in 5 mmHg bins. When MAP was within the autoregulation range, cerebral oximetry index and laser Doppler index approach 0, but when MAP is below the lower limit of autoregulation (arrow), these indices approach 1, indicating that cerebral blood flow is pressure-passive. In other words, laser Doppler flux and regional cerebral oxygen saturation as a surrogate of cerebral blood flow are directly related to MAP. A distinct advantage of the signal-filtered near infrared spectroscopy method is the continuous and noninvasive nature of its output, allowing ease of clinical implementation with minimal care-taker intervention.

Many clinical methods of autoregulation monitoring are performed by continuously evaluating the correlation between spontaneously occurring slow-wave changes in blood pressure and cerebral blood flow or cerebral vascular reactivity, thus avoiding the need to lower or raise blood pressure especially in patients who have compromised organ perfusion.<sup>27</sup> These latter methods require time to generate the autoregulation metrics that may inadvertently expose some patients to a MAP lower than the lower limit of autoregulation or greater than the upper limit of autoregulation. A variety of waveform analytics in addition to correlation have been used to model the filtering function of autoregulation, including the cross-correlation functions of coherence, phase, and gain of transfer. The combinations of output surrogates and mathematical functions that can be made are



**Fig. 1.** Validation of time-domain analysis method of cerebral autoregulation. In this piglet model, cerebral perfusion pressure was manipulated by inflation of a catheter-tipped balloon placed in the inferior vena cava. (A) Laser Doppler (IDoppler) flux–determined cerebral blood flow is plotted against cerebral perfusion pressure (CPP). The point of intersection of two linear regression lines marks the lower limit of autoregulation (lower limit of autoregulation) which is 34 mmHg in this piglet. (B) Near-infrared spectroscopy regional cerebral oxygen saturation is plotted against cerebral perfusion pressure. (C, D) Correlation coefficient between laser Doppler flux and cerebral perfusion pressure and near-infrared spectroscopy derived cerebral oximetry index with cerebral perfusion pressure. When mean arterial pressure is above the lower limit of autoregulation, there is low correlation between cerebral perfusion pressure and laser Doppler index (LDx) and cerebral oximetry index (COx), indicating that cerebral blood flow is independent of blood pressure or autoregulated. In contrast, when mean arterial pressure is lower than the lower limit of autoregulation (34 mmHg), laser Doppler index and cerebral oximetry index approach 1.0 as cerebral blood flow is blood pressure passive. Reprinted with permission from Brady *et al.*<sup>29</sup>

varied, and they render results that are variable.<sup>32</sup> Generating low-frequency (*i.e.*, 1/min) oscillations in blood pressure and evaluating the phase angle of the cerebral vascular response is one such approach. Blood pressure oscillations can be generated by simply increasing positive end-expiratory pressure by 5 cm H<sub>2</sub>O above background airway pressure once per minute.<sup>33</sup> Intact autoregulation results in cerebral vascular responses with a phase angle greater than 120° in relation to blood pressure oscillation. Blood pressure outside of the autoregulation range is manifest as a phase angle that is shorter. This method provides near instantaneous assessment of whether a given MAP is within the autoregulation range.

## Clinical Significance of Blood Pressure outside the Limits of Autoregulation

### Traumatic Brain Injury

The bulk of early clinical work in cerebral blood flow autoregulation monitoring occurred in neurocritically ill patients with traumatic brain injury.<sup>27</sup> The presence of ICP monitoring allows for the continuous bedside evaluation

of the pressure reactivity index (see above description of pressure reactivity index in the Monitoring Cerebral Blood Flow Autoregulation section) as a means for evaluating cerebral vasoreactivity, the mediator of cerebral blood flow autoregulation. Tracking the relationship between ICP and cerebral perfusion pressure allows for an assessment of whether the latter occurs independently or dependently with changes in ICP (intact autoregulation and impaired autoregulation, respectively). The term “optimal cerebral perfusion pressure” was introduced to denote that cerebral perfusion pressure with the most robust autoregulation.<sup>34</sup> In a retrospective study of 327 patients with traumatic brain injury, cerebral perfusion pressure below the optimal pressure was associated with mortality, whereas cerebral perfusion pressure above optimal pressure was associated with risk of functional disability.<sup>34</sup> In a systematic review and meta-analysis, our group compared different autoregulation indices for predicting patient outcomes from traumatic brain injury.<sup>35</sup> Based on data from 924 patients in 20 publications, the pressure reactivity index, mean velocity index, and autoregulation reactivity index were the strongest

predictors of mortality or Glasgow Outcome Scale at 3 to 6 months (z scores of 8.97, 6.01, and 3.94, respectively). In that review, there were fewer studies of patients with acute ischemic stroke, intracranial hemorrhage, or subarachnoid hemorrhage. There was a correlation between the duration of monitoring and the predictive value for mortality.

### Complications after Cardiac Surgery

Ensuring brain perfusion during cardiac surgery as assessed with near-infrared spectroscopy monitoring regional cerebral oxygen saturation has been argued to be a practical approach to ensure organ perfusion in addition to the brain.<sup>36</sup> We have performed a series of studies using our prospectively collected database evaluating whether excursion of MAP outside the limits of autoregulation assessed with regional cerebral oxygen saturation derived cerebral oximetry index monitoring during cardiac surgery impacts risk for postoperative complications. In a study of 410 patients undergoing cardiac surgery, we determined the relationship between the area under the curve in which MAP was lower than the lower limit of autoregulation during CPB and postoperative acute kidney injury.<sup>37,38</sup> We found that the area under the curve in which MAP was lower than the lower limit of autoregulation was higher for the 34.8% of patients with acute kidney injury compared with those without acute kidney injury. In risk adjusted analysis, the area under the curve in which MAP was lower than the lower limit of autoregulation predicted acute kidney injury (relative risk, 1.02; 95% CI, 1.01 to 1.04;  $P = 0.001$ ). The risk for acute kidney injury was 10% (95% CI, 7.2% to 18.8%) for each 5 mmHg  $\times$  h of MAP below the lower limit of autoregulation.

Because mortality is relatively low after cardiac surgery, major organ complications are often reported as a means of assessing surgical quality.<sup>39</sup> We performed an analysis to evaluate whether there is a relationship between MAP lower than the lower limit of autoregulation during CPB and major morbidity or mortality after cardiac surgery.<sup>40</sup> The latter composite outcome was defined as death within 30 days of surgery, stroke, renal failure (new requirement for dialysis postoperatively or an increase in creatinine to more than 2mg/dl and two times greater than baseline), mechanical lung ventilation for more than 48h after

surgery, or low cardiac output syndrome. The primary composite endpoint of the study was observed in 83 (18.4%) of 450 patients. The area under the curve in which MAP was lower than the lower limit of autoregulation during CPB was independently associated with major morbidity or operative mortality (odds ratio, 1.36; 95% CI, 1.08 to 1.71;  $P = 0.008$ ). Evaluation of the component variables of the composite outcome demonstrated that the area under the curve in which MAP was lower than the lower limit of autoregulation was larger in patients with stroke ( $P = 0.056$ ), renal failure ( $P = 0.03$ ), and prolonged mechanical lung ventilation ( $P < 0.001$ ) compared with patients without this complication. The MAP lower than the lower limit of autoregulation for patients with and without organ injury is shown in table 2.

### Postoperative Brain Dysfunction

Simply raising contemporary MAP targets during surgery may result in a MAP that is higher than the upper limit of autoregulation in some patients. In this situation, cerebral blood flow will increase proportionally with MAP, potentially leading to cerebral hyperperfusion, a situation that is associated with cerebral edema and brain dysfunction in nonsurgical patients.<sup>41</sup> In a study of 303 patients undergoing cardiac surgery with CPB, an upper limit of cerebral autoregulation was observed in 62% patients.<sup>42</sup> In the other 38%, we surmise that MAP never achieved this threshold. The MAP at the upper threshold of cerebral blood flow autoregulation was (mean  $\pm$  SD)  $90 \pm 12$  mmHg (95% CI, 88 to 91 mmHg). The area under the curve in which MAP was lower than the lower limit of autoregulation was larger in patients with clinically detected delirium compared with those not having delirium. However, the area under the curve in which MAP is lower than the lower limit of autoregulation was no longer predictive of delirium when the logistic model included the area under the curve that MAP was higher than the upper limit of autoregulation. In the latter model, the area under the curve in which MAP was greater than the upper limit of autoregulation was independently associated with clinical delirium (odds ratio, 1.09; 95% CI, 1.03 to 1.15).

**Table 2.** MAP at the LLA during Cardiopulmonary Bypass

	Complication Present	Complication Not Present	P Value
Acute kidney injury			
MAP at the LLA (mmHg)	69 $\pm$ 16 (66–72)	63 $\pm$ 15 (61–65)	0.001
AUC <sub>MAP&lt;LLA</sub> (mmHg $\times$ min/h)	11.2 (7.8–13.0)	6.6 (5.7–7.9)	0.014
Major morbidity or operative mortality			
MAP at the LLA (mmHg)	71 $\pm$ 12 (67–72)	69 $\pm$ 14 (67–70)	0.136
AUC <sub>MAP&lt;LLA</sub> (mmHg $\times$ min/h)	6.5 (2.1–15.4)	2.4 (1.1–5.7)	0.017

Mean arterial pressure (MAP) at the lower limit of cerebral blood flow autoregulation (LLA) during cardiopulmonary bypass for those patients suffering acute kidney injury or major morbidity or operative mortality after surgery.<sup>37,40</sup> The area under the curve (AUC) in which MAP was below the LLA is listed.

## Postoperative ICU Blood Pressure Linked to Brain Injury Biomarker Release

Patients recovering from cardiac surgery in the ICU remain at risk for hypotension. We performed a retrospective study in 121 patients recovering after cardiac surgery in the ICU evaluating the relationship between a MAP lower than the lower limit of autoregulation and brain cellular injury.<sup>43</sup> Brain injury was assessed by the measurement of plasma concentrations of the brain-specific injury biomarker glial fibrillary acidic protein. In 65 (53.7%) patients, the average MAP in the ICU was lower than the optimal autoregulation range (*i.e.*, that MAP where autoregulation was the most robust or had the lowest cerebral oximetry index value). After adjusting for plasma glial fibrillary acid protein levels at the end of surgery, the product of the magnitude and duration that MAP was lower than optimal in the ICU was correlated with plasma glial fibrillary acid protein levels measured on postoperative day 1 (coefficient, 1.77; 95% CI, 1.27 to 2.48;  $P = 0.001$ ). Empiric blood pressure cutoffs for defining hypotension (*i.e.*, systolic blood pressure of less than 20%, less than 30% of awake baseline, and/or systolic blood pressure less than 100 mmHg) were not related to postoperative plasma glial fibrillary acid protein.

## Reducing Postoperative Delirium with Personalized MAP Targets

Our previous retrospective analyses have identified an association between the area under the curve that MAP was outside the limits of autoregulation and postoperative complications but not causality. To better evaluate the importance of hypotension in patient outcomes from cardiac surgery, we have recently completed a prospectively, randomized, single-blinded study where MAP during CPB was targeted to be greater than the lower limit of autoregulation *versus* the usual institutional care where MAP targets were empirically chosen (clinicaltrials.gov registration, NCT00981474). A subset of 199 patients enrolled in that trial underwent detailed assessments for postoperative delirium.<sup>44</sup> We found that the odds of delirium was reduced by 45% in the group whose MAP target were determined by autoregulation monitoring compared with the usual care (odds ratio, 0.55; 95% CI, 0.31 to 0.97;  $P = 0.04$ ). Although preliminary, these data suggest that optimizing MAP to be higher than an individual's lower limit of autoregulation, but lower than the upper limit, during CPB may be a strategy to reduce the frequency of postoperative delirium.

## Monitoring Autoregulation in Noncardiac Surgery

Our work has primarily focused on cardiac surgery patients where an arterial catheter is available for direct blood pressure monitoring. Our methods involve correlating low frequency changes in cerebral blood flow with MAP not systolic or diastolic blood pressure. Thus, because our data are based on MAP, the low pulsatile state of CPB should

not largely limit extrapolation of our findings to other situations. We have, in fact, shown that cerebral blood flow autoregulation is preserved after implantation of a nonpulsatile left ventricular device.<sup>45</sup> We have also reported cerebral blood flow autoregulation monitoring in noncardiac surgery using continuous arterial pressure readings derived from noninvasive finger plethysmography (Finometer Pro, Finapres Medical Systems, The Netherlands).<sup>19,46</sup> In patients having shoulder surgery, the MAP at the lower limit of autoregulation was 65 mmHg (25th to 75th percentile, 55 to 75) in patients who remained supine and 70 mmHg (25th to 75th percentile, 55 to 80) for patients in the beach chair position. Patients in the beach chair position were more likely to have autoregulation suggestive of MAP below the lower limit of autoregulation during surgery than those undergoing surgery in the lateral decubitus position.

## Clinical Approach to Defining Hypotension

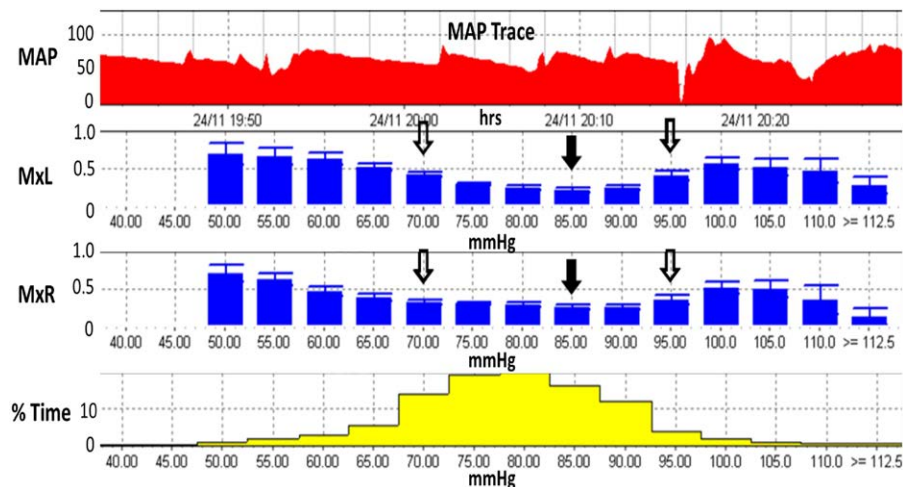
There are several important principles that clinicians must acknowledge when defining intraoperative hypotension. First, the ultimate impact of any blood pressure cutoff for defining hypotension on organ function is dependent on its duration (table 1). Thus, a MAP of less than 65 mmHg for a long duration might result in ischemic organ damage similar in extent to a MAP of less than 40 mmHg of shorter duration. Second, organ blood flow reserve might protect from direct organ injury from a MAP below the autoregulation limit. With respect to the brain, the concept of central nervous system (CNS) blood flow reserve may explain the discrepancy between resting cerebral blood flow and the cerebral blood flow in which symptoms of cerebral hypoperfusion occur.<sup>47</sup> In healthy, nonanesthetized subjects, the brain can tolerate a 35% to 40% reduction in cerebral blood flow before cerebral symptoms occur.<sup>47</sup> Thus, a MAP lower than the lower limit of autoregulation may not necessarily lead to CNS injury until cerebral blood flow is below the limits of CNS flow reserve such as in clinical situations of permissive hypotension. Sedated, anesthetized, or critically ill patients, however, cannot convey symptoms of cerebral hypoperfusion. Moreover, the individual lower limit of autoregulation or cerebral blood flow global or regional threshold for CNS ischemia is not known and likely influenced by many factors that are not clinically manifest. The latter include covert brain infarctions, especially lacunar infarctions, or the onset of cerebral edema as has been reported with brain magnetic resonance imaging immediately after cardiac surgery.<sup>48</sup> We have found a relationship between the cerebral white matter disease determined with brain magnetic resonance imaging, an indicator of cerebral small vessel disease, and impaired cerebral blood flow autoregulation.<sup>49</sup> Thus, although patients may variably tolerate blood pressure lower than the lower limit of autoregulation or higher than the upper limit of autoregulation, particularly if of brief duration, precisely knowing these cutoff in the operating room or ICU would seem more precise for managing blood pressure than population-based summary estimates.

Our autoregulation studies have emphasized MAP and not cerebral perfusion pressure (*i.e.*, MAP minus ICP or central venous pressure, whichever is higher) because suction-assisted venous drainage during CPB results in a low central venous pressure. Cerebral perfusion pressure and not MAP *per se* should be considered in situations where ICP or central venous pressure is elevated. Experimentally, elevated ICP is associated with a nonlinear right-ward shift of the lower limit of autoregulation. In a clinical study of infants with a cavopulmonary anastomosis, elevated CVP (*e.g.*, cavopulmonary pressure) was associated with autoregulatory failure.<sup>50,51</sup> In our studies the end-tidal concentrations of volatile anesthetics have been lower than 1 minimum alveolar concentration. Higher concentrations of volatile anesthetics can shorten the autoregulation plateau, whereas intravenous anesthetics do not have this effect.<sup>52</sup>

Thus far, our group has (1) validated clinically feasible methods of cerebral blood flow autoregulation in laboratory animals and humans; (2) demonstrated a relationship between a MAP outside the autoregulation boundaries and brain dysfunction and other organ injury; and (3) shown that acting on MAP that is lower than the lower limit of autoregulation during cardiac surgery reduces the frequency of delirium after surgery.<sup>17,29,37,40,42–44</sup> We acknowledge that the majority of our clinical findings linking MAP outside the limits of autoregulation and adverse patient outcomes have been in

the setting of cardiac surgery, and these results may not necessarily be easily extrapolated to other noncardiac surgery settings. Certainly, more research is necessary to confirm and extend our results. Importantly, a barrier to implementation of cerebral blood flow autoregulation monitoring presently is the lack of a Food and Drug Administration–approved monitor. We have demonstrated the feasibility of such a “plug-and-play” near-infrared spectroscopy–based autoregulation monitor that could be made commercially available.<sup>53</sup>

Nonetheless, in the absence of a clinically available autoregulation monitor, some inferences for hemodynamic management can be derived from existing data. We have found that the “optimal MAP” (*i.e.*, MAP with the most robust autoregulation or the lowest mean velocity index) during CPB in adults is (mean ± SD) 78 ± 11 mmHg (fig. 2).<sup>54</sup> The results of our studies of 617 patients undergoing cardiac surgery found that the average (±SD) lower limit of autoregulation was 65 ± 12 mmHg, and the average upper limit of autoregulation was 84 ± 11 mmHg. Of interest, variables independently associated with optimal MAP based on multivariate regression analysis were nonwhite race (increased 2.7 mmHg; *P* = 0.034); diuretic use (decreased 1.9 mmHg, *P* = 0.049); prior carotid endarterectomy (decreased 5.5 mmHg, *P* = 0.019); and duration of CPB (decreased 1.28 mmHg per 60 min, *P* = 0.022) but not patient age or medical history, including hypertension.



**Fig. 2.** Intraoperative recording from a single patient. The top is mean arterial pressure (MAP), the second and third mean velocity index for the left (MxL) and right (MxR) middle cerebral arteries, and the bottom the percentage of the time of the recording spent at each 5 mmHg MAP bin. Mean velocity index is derived as the Pearson correlation coefficient between low-frequency (less than 0.05 Hz) changes in cerebral blood flow velocity measured with transcranial Doppler and MAP. When blood pressure is within the autoregulation range, there is a low correlation between cerebral blood flow velocity and MAP resulting in a mean velocity index close to 0 (bar graphs in 5 mmHg bins). That is, MAP changes occur without corresponding changes in cerebral blood flow because autoregulation is functional. When MAP is below or above the autoregulation limits, the mean velocity index approaches 1, or decreases or increases in MAP, respectively, are correlated with cerebral blood flow velocity. In this figure the *open arrows* represent the arbitrary lower and upper limits of autoregulation using an arbitrary cutoff of an increase in mean velocity index of at least 0.4 declining or increases in MAP. The *solid arrows* indicate MAP where mean velocity index is the lowest, representing the optimal MAP, or MAP with the most robust autoregulation. Note the natural fluctuations in MAP that occur during the normal conduct of surgery in the time series of arterial pressures in the top.

For patients undergoing noncardiac shoulder surgery, our data suggest that the lower limit of autoregulation in most patients is a MAP between 65 and 70 mmHg. These data are consistent with the results of the systematic review of observational, database reviews linking MAP cutoffs and organ injury (table 1). Our findings are further consistent with the conclusion in a recent review by Drummond,<sup>47</sup> who emphasized the need to consider the projected blood pressure at the circle of Willis when the head is elevated above the horizontal as for surgery in the beach chair position (*i.e.*, subtract 1 mmHg per 1.35 cm of head elevation from blood pressure measured from arm or leg). Although these sound recommendations might apply to the majority of patients, there will be patients whose lower limit of autoregulation or upper limit of autoregulation are outside of these ranges.

## Conclusions

After more than a century of the measurement of blood pressure during general anesthesia, clinicians now have a potential tool for personalizing the definition of hypotension based on cerebral blood flow autoregulation monitoring. Current data point to the limitations of using a single blood pressure cutoff for a wide population of patients because the individual's lower limit of autoregulation may or may not be above this arbitrary cutoff. Nonetheless, clinicians are presently forced to use this approach for determining the lowest tolerable blood pressure for a given patient in until a Food and Drug Administration–approved monitor is available that will provide individual autoregulation data at the bedside.

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## Competing Interests

Dr. Hogue has served as a consultant and has provided lectures for Medtronic, Inc., Minneapolis, Minnesota, and Edwards Lifesciences, Irvine, California. The other authors declare no competing interests.

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## References

1. Cushing H: On routine determination of arterial tension in operating room and clinic. *Boston Med Surgical J* 1903; 148:250–6
2. Sundararaman LV, Desai SP: The anesthesia records of Harvey Cushing and Ernest Codman. *Anesth Analg* 2018; 126:322–9
3. McKesson E: The reaction of certain circulatory conditions to anesthesia and surgery. *Anesth Analg* 1923; 2:43–9
4. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ: Incidence of intraoperative hypotension as a function of the chosen definition: Literature definitions applied to a retrospective cohort using automated data collection. *ANESTHESIOLOGY* 2007; 107:213–20
5. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA: Intraoperative hypotension and the risk of postoperative adverse outcomes: A systematic review. *Br J Anaesth* 2018; 121:706–21
6. Reich DL, Bodian CA, Krol M, Kuroda M, Osinski T, Thys DM: Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. *Anesth Analg* 1999; 89:814–22
7. Rettig TCD, Peelen LM, Geuzebroek GSC, van Klei WA, Boer C, van der Veer JW, Hofland J, van de Garde EMW, Noordzij PG: Impact of intraoperative hypotension during cardiopulmonary bypass on acute kidney injury after coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 2017; 31:522–8
8. Gottesman RF, Sherman PM, Grega MA, Yousem DM, Borowicz LM Jr, Selnes OA, Baumgartner WA, McKhann GM: Watershed strokes after cardiac surgery: Diagnosis, etiology, and outcome. *Stroke* 2006; 37:2306–11
9. Sun LY, Chung AM, Farkouh ME, van Diepen S, Weinberger J, Bourke M, Ruel M: Defining an intraoperative hypotension threshold in association with stroke in cardiac surgery. *ANESTHESIOLOGY* 2018; 129:440–7
10. Gold JP, Charlson ME, Williams-Russo P, Szatrowski TP, Peterson JC, Pirraglia PA, Hartman GS, Yao FS, Hollenberg JP, Barbut D: Improvement of outcomes after coronary artery bypass: A randomized trial comparing intraoperative high *versus* low mean arterial pressure. *J Thorac Cardiovasc Surg* 1995; 110:1302–14



11. Siepe M, Pfeiffer T, Gieringer A, Zemann S, Benk C, Schlensak C, Beyersdorf F: Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. *Eur J Cardiothorac Surg* 2011; 40:200–7
12. Wesselink EM, Kappen TH, van Klei WA, Dieleman JM, van Dijk D, Slooter AJ: Intraoperative hypotension and delirium after on-pump cardiac surgery. *Br J Anaesth* 2015; 115:427–33
13. Vedel AG, Holmgaard F, Rasmussen LS, Langkilde A, Paulson OB, Lange T, Thomsen C, Olsen PS, Ravn HB, Nilsson JC: High-target *versus* low-target blood pressure management during cardiopulmonary bypass to prevent cerebral injury in cardiac surgery patients: A randomized controlled trial. *Circulation* 2018; 137:1770–80
14. Brady K, Easley R, Bissonnette B: Developmental physiology of the central nervous system, Gregory's Pediatric Anesthesia, 5th edition. Edited by Gregory G, Andropoulos D. Hoboken, New Jersey, Wiley-Blackwell, 2011, pp 117–38
15. Lassen NA: Cerebral blood flow and oxygen consumption in man. *Physiol Rev* 1959; 39:183–238
16. Drummond JC: The lower limit of autoregulation: Time to revise our thinking? *ANESTHESIOLOGY* 1997; 86:1431–3
17. Brady KM, Mytar JO, Lee JK, Cameron DE, Vricella LA, Thompson WR, Hogue CW, Easley RB: Monitoring cerebral blood flow pressure autoregulation in pediatric patients during cardiac surgery. *Stroke* 2010; 41:1957–62
18. Joshi B, Ono M, Brown C, Brady K, Easley RB, Yenokyan G, Gottesman RF, Hogue CW: Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. *Anesth Analg* 2012; 114:503–10
19. Laflam A, Joshi B, Brady K, Yenokyan G, Brown C, Everett A, Selnes O, McFarland E, Hogue CW: Shoulder surgery in the beach chair position is associated with diminished cerebral autoregulation but no differences in postoperative cognition or brain injury biomarker levels compared with supine positioning: The Anesthesia Patient Safety Foundation beach chair study. *Anesth Analg* 2015; 120:176–85
20. Rhee CJ, Kibler KK, Easley RB, Andropoulos DB, Czosnyka M, Smielewski P, Brady KM: Renovascular reactivity measured by near-infrared spectroscopy. *J Appl Physiol* (1985) 2012; 113:307–14
21. Meng L, Hou W, Chui J, Han R, Gelb AW: Cardiac output and cerebral blood flow: The integrated regulation of brain perfusion in adult humans. *ANESTHESIOLOGY* 2015; 123:1198–208
22. Schwartz AE, Sandhu AA, Kaplon RJ, Young WL, Jonassen AE, Adams DC, Edwards NM, Sestino JJ, Kwiatkowski P, Michler RE: Cerebral blood flow is determined by arterial pressure and not cardiopulmonary bypass flow rate. *Ann Thorac Surg* 1995; 60:165–70
23. Govier AV, Reves JG, McKay RD, Karp RB, Zorn GL, Morawetz RB, Smith LR, Adams M, Freeman AM: Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. *Ann Thorac Surg* 1984; 38:592–600
24. Nusbaum DM, Brady KM, Kibler KK, Blaine Easley R: Acute hypercarbia increases the lower limit of cerebral blood flow autoregulation in a porcine model. *Neurol Res* 2016; 38:196–204
25. Finnerty FA Jr, Witkin L, Fazekas JF: Cerebral hemodynamics during cerebral ischemia induced by acute hypotension. *J Clin Invest* 1954; 33:1227–32
26. Brady KM, Mery CM: Cerebral autoregulation: Making sense of the nonsensical. *J Thorac Cardiovasc Surg* 2017; 154:1045–6
27. Czosnyka M, Brady K, Reinhard M, Smielewski P, Steiner LA: Monitoring of cerebrovascular autoregulation: Facts, myths, and missing links. *Neurocrit Care* 2009; 10:373–86
28. Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, Pickard JD: Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med* 2002; 30:733–8
29. Brady KM, Lee JK, Kibler KK, Smielewski P, Czosnyka M, Easley RB, Koehler RC, Shaffner DH: Continuous time-domain analysis of cerebrovascular autoregulation using near-infrared spectroscopy. *Stroke* 2007; 38:2818–25
30. Lee JK, Kibler KK, Benni PB, Easley RB, Czosnyka M, Smielewski P, Koehler RC, Shaffner DH, Brady KM: Cerebrovascular reactivity measured by near-infrared spectroscopy. *Stroke* 2009; 40:1820–6
31. Zeiler FA, Donnelly J, Menon DK, Smielewski P, Zweifel C, Brady K, Czosnyka M: Continuous autoregulatory indices derived from multi-modal monitoring: Each one is not like the other. *J Neurotrauma* 2017; 34:3070–80
32. Zeiler FA, Donnelly J, Calviello L, Lee JK, Smielewski P, Brady K, Kim DJ, Czosnyka M: Validation of pressure reactivity and pulse amplitude indices against the lower limit of autoregulation: Part I. Experimental intracranial hypertension. *J Neurotrauma* 2018; 35:2803–11
33. Brady KM, Easley RB, Kibler K, Kaczka DW, Andropoulos D, Fraser CD 3rd, Smielewski P, Czosnyka M, Adams GJ, Rhee CJ, Rusin CG: Positive end-expiratory pressure oscillation facilitates brain vascular reactivity monitoring. *J Appl Physiol* (1985) 2012; 113:1362–8
34. Aries MJ, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Koliass AG, Hutchinson PJ, Brady KM, Menon DK, Pickard JD, Smielewski P: Continuous

- determination of optimal cerebral perfusion pressure in traumatic brain injury. *Crit Care Med* 2012; 40:2456–63
35. Rivera-Lara L, Zorrilla-Vaca A, Geocadin R, Ziai W, Healy R, Thompson R, Smielewski P, Czosnyka M, Hogue CW: Predictors of outcome with cerebral autoregulation monitoring: A systematic review and meta-analysis. *Crit Care Med* 2017; 45:695–704
  36. Murkin JM, Arango M: Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br J Anaesth* 2009; 103:i3–13
  37. Ono M, Arnaoutakis GJ, Fine DM, Brady K, Easley RB, Zheng Y, Brown C, Katz NM, Grams ME, Hogue CW: Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. *Crit Care Med* 2013; 41:464–71
  38. Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettilä V: Acute renal failure after cardiac surgery: Evaluation of the RIFLE classification. *Ann Thorac Surg* 2006; 81:542–6
  39. Shroyer AL, Coombs LP, Peterson ED, Eiken MC, DeLong ER, Chen A, Ferguson TB, Jr., Grover FL, Edwards FH, Society of Thoracic Surgeons: The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. *Ann Thorac Surg* 2003; 75:1856–65
  40. Ono M, Brady K, Easley RB, Brown C, Kraut M, Gottesman RF, Hogue CW Jr: Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. *J Thorac Cardiovasc Surg* 2014; 147:483–9
  41. Miller JB, Suchdev K, Jayaprakash N, Hrabec D, Sood A, Sharma S, Levy PD: New developments in hypertensive encephalopathy. *Curr Hypertens Rep* 2018; 20:13
  42. Hori D, Brown C, Ono M, Rappold T, Sieber F, Gottschalk A, Neufeld KJ, Gottesman R, Adachi H, Hogue CW: Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. *Br J Anaesth* 2014; 113:1009–17
  43. Hori D, Ono M, Rappold TE, Conte JV, Shah AS, Cameron DE, Adachi H, Everett AD, Hogue CW: Hypotension after cardiac operations based on autoregulation monitoring leads to brain cellular injury. *Ann Thorac Surg* 2015; 100:487–93
  44. Brown CI, Neufeld K, Tian J, Probert J, Laflam A, Max L, Hori D, Nomura Y, Mandal K, Brady K, Hogue C: Targeting mean arterial pressure during cardiopulmonary bypass using cerebral autoregulation monitoring to reduce delirium. *JAMA Surg* 2019; 154:819–26
  45. Ono M, Joshi B, Brady K, Easley RB, Kibler K, Conte J, Shah A, Russell SD, Hogue CW: Cerebral blood flow autoregulation is preserved after continuous-flow left ventricular assist device implantation. *J Cardiothorac Vasc Anesth* 2012; 26:1022–8
  46. Lavinio A, Schmidt EA, Haubrich C, Smielewski P, Pickard JD, Czosnyka M: Noninvasive evaluation of dynamic cerebrovascular autoregulation using Finapres plethysmograph and transcranial Doppler. *Stroke* 2007; 38:402–4
  47. Drummond JC: Blood pressure and the brain: How low can you go? *Anesth Analg* 2019; 128:759–71
  48. Harris DN, Bailey SM, Smith PL, Taylor KM, Oatridge A, Bydder GM: Brain swelling in first hour after coronary artery bypass surgery. *Lancet* 1993; 342:586–7
  49. Nomura Y, Faegle R, Hori D, Al-Qamari A, Nemeth AJ, Gottesman R, Yenokyan G, Brown C, Hogue CW: Cerebral small vessel, but not large vessel disease, is associated with impaired cerebral autoregulation during cardiopulmonary bypass: A retrospective cohort study. *Anesth Analg* 2018; 127:1314–22
  50. Nusbaum D, Clark J, Brady K, Kibler K, Sutton J, Easley RB: Alteration in the lower limit of autoregulation with elevations in cephalic venous pressure. *Neurol Res* 2014; 36:1063–71
  51. Cabrera AG, Kibler KK, Blaine Easley R, Goldsworthy M, Shekerdemian LS, Andropoulos DB, Heinle J, Gottlieb EA, Vu E, Brady KM: Elevated arterial blood pressure after superior cavo-pulmonary anastomosis is associated with elevated pulmonary artery pressure and cerebrovascular dysautoregulation. *Pediatr Res* 2018; 84:356–61
  52. Patel P, Drummond J: *Cerebral Physiology and the Effects of Anesthetics and Techniques*, 6th edition. Philadelphia, Pennsylvania, Elsevier Churchill Livingstone, 2005
  53. Ono M, Zheng Y, Joshi B, Sigl JC, Hogue CW: Validation of a stand-alone near-infrared spectroscopy system for monitoring cerebral autoregulation during cardiac surgery. *Anesth Analg* 2013; 116:198–204
  54. Hori D, Nomura Y, Ono M, Joshi B, Mandal K, Cameron D, Kocherginsky M, Hogue CW: Optimal blood pressure during cardiopulmonary bypass defined by cerebral autoregulation monitoring. *J Thorac Cardiovasc Surg* 2017; 154:1590–8