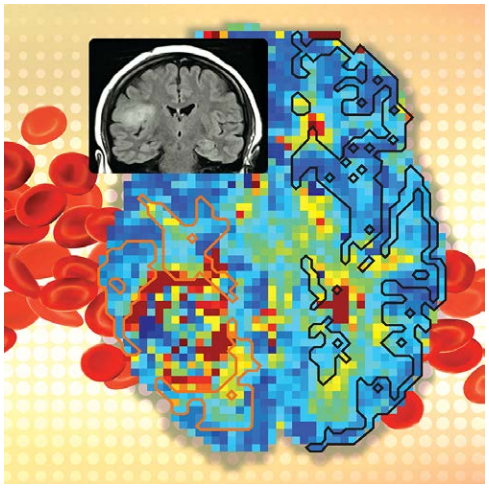
Phenylephrine or Ephedrine for Intraoperative Hypotension? Consider the Cerebral Microcirculation

Paul S. García, M.D., Ph.D., Charles H. Brown IV, M.D., M.H.S.

Intraoperative hypotension is common and known to be associated with suboptimal patient outcomes.[1] Over 90% of patients receiving anesthesia for surgery are expected to have at least one documented episode where the blood pressure decreased more than 20% below baseline.[2] Although several factors may be involved in choosing a pharmacologic intervention for intraoperative hypotension in the absence of arrythmia (*e.g.*, volume status, clinical effect of induction and maintenance anesthetics, anticipation of intense surgical stimulation), vasopressor support is often chosen as an efficient and convenient way to raise the blood pressure.

In this issue, Koch *et al.* present a randomized controlled trial that compares the effects of our two most common agents for vasopressor support, phenylephrine and ephedrine, on characteristics of macro- and microcirculation.[3] In this study, anesthetized brain tumor patients were randomly assigned to receive ephedrine or phenylephrine infusions while receiving magnetic resonance imaging pre- and postinfusion initiation. Despite similar blood pressure endpoints (macrocirculation), ephedrine infusion resulted in improved cerebral blood flow and tissue perfusion. Phenylephrine infusion demonstrated greater heterogeneity in capillary transit time in the hemisphere contralateral to the lesion—suggesting a deterioration of cerebral microcirculation (*i.e.*, at the level of arterioles and capillaries). These findings provide additional information for anesthesiologists to consider while deciding on appropriate pharmacologic treatments for intraoperative hypotension.



"…despite roughly equivalent effects on macrocirculation in patients with brain tumors, phenylephrine may worsen cerebral microcirculation and tissue oxygen extraction as compared to ephedrine."

As anesthesiologists and critical care physicians, we carefully titrate our management to hemodynamic parameters that we can measure (*i.e.*, parameters of macrocirculation), and historically, maintenance of mean arterial pressure greater than 65 mmHg and pulse oxygen saturation greater than 92% have been considered adequate. Additional parameters that can be measured and titrated include cardiac index, systemic vascular resistance, and hemoglobin concentration. Although the importance of macrocirculation is clear, microcirculatory abnormalities may also profoundly impair adequate perfusion, even with optimal macrocirculation parameters. This is particularly relevant for cerebral perfusion during cardiac surgery as well as noncardiac surgery in elderly patients since many of these patients will have underlying cerebrovascular disease.

Unfortunately, because microcirculatory parameters are not routinely measured in clinical care, we are often ignorant of whether we actually achieve the primary goals of maintaining adequate tissue perfusion and oxygen utilization. The results of the current study suggest a differential effect of phenylephrine and ephedrine on microcirculatory parameters in patients with brain tumors. Whether these findings have impact on clinical outcomes in a broader clinical context is unclear.

Currently, intraoperative magnetic resonance imaging remains impractical for aiding in pharmacologic decisions in real time, and undertaking a comprehensive clinical trial over a wide range of patients using this modality to examine microcirculation would be at substantial expense. However, the study highlights that improved monitoring

Image: A. Johnson, Vivo Visuals Studio.

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approaches are needed to ensure adequate cerebral perfusion beyond traditional hemodynamic parameters that reflect the macrocirculation.

One monitor that is routinely used to assess cerebral perfusion during cardiac surgery is cerebral oximetry. It reflects the balance between oxygen supply and utilization in a local region of the frontal cortex. There is reasonable evidence that baseline cerebral oximetry values are associated with mortality after cardiac surgery,[4,5] and agreement that unilateral acute decreases in cerebral oximetry values during surgery indicate a high potential for cerebral ischemia.[6] However, the evidence is less strong that routine hemodynamic management based on cerebral oximetry values improves outcomes. In the current study, regional cerebral oxygen saturation values generally declined with vasopressor treatment (with the decline in the phenylephrine group greater than in the ephedrine group), but there was no statistical difference between the vasopressor treatment groups. Thus, the authors conclude that regional cerebral oxygen saturation values did not reflect changes in cerebral blood flow or oxygen metabolism induced by ephedrine. These findings, in combination with a previous paper reporting that cerebral oxygen saturation values did not reflect changes in cerebral metabolic rate of oxygen after ephedrine administration,[7] highlight limitations in the use of current cerebral oximetry monitors and support the need for more spatiotemporal precision in monitoring cerebral perfusion and oxygen utilization. Perhaps as technology improves regarding functional near-infrared spectroscopy, these noninvasive devices might be employed as a real-time monitor of neurovascular coupling in the perioperative space.[8]

A second monitor that is routinely employed during surgery is the Bispectral Index (BIS) monitor. In the current study, BIS monitoring was used for titrating roughly equipotent doses of propofol and remifentanil, and the authors observed no differences in BIS or drug concentrations between groups. These monitors based on electroencephalogram (EEG) recordings might aid in diagnosing the etiology of intraoperative hypotension and therefore influence therapeutic decisions to treat hypotension. Here again, though, limitations of our current brain monitoring technology do not provide information on microcirculation. Processed EEG indices are notoriously bad at identifying discontinuous EEG patterns[9] known to be associated with impaired neurovascular coupling[10] and worse postoperative outcomes,[11,12] in part because ischemia on the EEG may represent profound failure in cerebral perfusion with inadequate compensatory mechanisms. Despite increasing interest in combining EEG information with knowledge from analgesic pharmacology, sleep, and systems neuroscience, standards for monitoring the end-target organ of our anesthetic medication remain elusive.[13] Unfortunately, a minority of anesthesiologists feel comfortable making clinical decisions based on visual inspection of the raw EEG time-series, and standards for training/certification in intraoperative pharmacologic decision-making based on interpretation of quantitative EEG have yet to be established. Investigations continue to focus on neurophysiologic changes that reliably predict patients at increased risk for adverse neurocognitive outcomes—yet we are lacking evidence that scalp EEG can aid in identifying problems with brain tissue oxygenation. Quantitative features beyond frequency analysis (*i.e.*, symmetry, phase, entropy, and coherence), higher-resolution EEG montages, and magnetoencephalogram techniques may hold promise in improving discrimination of specific intraoperative neurophysiologic changes[14] that might track with impairments in microcirculation.

There were weaknesses in the study design that are important to consider. As expected, differences in heart rate were present between the study groups, and obvious heart rate changes could cause inadvertent unblinding, although importantly, randomization was blinded to the persons analyzing the magnetic resonance imaging data. The study size was also small, and all patients had brain tumors, which might affect blood–brain barrier function. Nevertheless, the essential message from this study is that despite roughly equivalent effects on macrocirculation in patients with brain tumors, phenylephrine may worsen cerebral microcirculation and tissue oxygen extraction as compared to ephedrine. Other benefits of ephedrine infusion as compared to phenylephrine were increased cerebral blood flow to both hemispheres (lesion/nonlesion), decreased mean transit time, and higher oxygen tension. The results of this small study provide important information on pharmacologic influences on microcirculatory parameters. Although some might be tempted to extrapolate the results of this study to common scenarios we encounter daily in our own clinical practice, it is clearly premature to eliminate phenylephrine from our vasopressor arsenal. Perhaps if microcirculation parameters are easier to assess intraoperatively and shown to be relevant to postoperative outcomes, we can comprehensively determine how to deliver the correct vasopressor in the correct clinical situation.

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Competing Interests

Dr. García is a named inventor on several patents owned by Columbia University (New York, New York) related to visualization of EEG data. Dr. Brown has a data sharing agreement with Medtronic (Minneapolis, Minnesota).

Correspondence

Address correspondence to Dr. García: pg2618@cumc.columbia.edu

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