be treated with caution. However, randomized controlled trials are not always practical or ethical, and there are instances when reliable evidence has been obtained from observational studies. A striking example is research demonstrating the efficacy of condoms in preventing human immunodeficiency virus transmission. In the case of POCD, without collaborating with existing longitudinal studies of aging such as Alzheimer Disease Research Centers, it would be impractical to enroll a large cohort and conduct frequent neurocognitive assessments prospectively on subjects who may have surgery in the future. Moreover, for most surgeries, it would be unethical to randomize patients to surgery or control solely based on the soft evidence for POCD. We applaud Dr. Nainar et al. for their conclusion that our study should not hinder research; it should encourage scrupulous follow-up studies designed to support, refute, or refine our preliminary findings. To this end, we are pursuing a multicenter Alzheimer Disease Research Center-linked study and would welcome interested collaborators. Future studies should rigorously reexamine whether elderly patients experience early POCD and, further, whether there are specific patients undergoing specific surgeries who are susceptible to persistent POCD that is attributable to surgical events.

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High-dose Phenylephrine and Ephedrine in Obstetrics: Proving the Holy Grail Requires More Data

To the Editor: Dr. Smiley’s supportive editorial, Burden of Proof, prompted me to eagerly read the obstetric article by Dr. Ngan Kee et al., hoping to find the promised “Holy Grail” of obstetric anesthetic blood pressure control.1,2 Instead, I found a questionable clinical methodology of high-dose vasopressor therapy for American Society of Anesthesiologists 1–2 delivery under bupivacaine spinals with limited scientific disclosure of data, burdening me to ask, where is the proof and how is it pertinent to standard clinical methods?

1. Intravenous prehydration was withheld, and total fluid was limited to 2 l during the 27 min to delivery.
2. Immediately, preoperatively obtained oscillotonometric systolic pressures were chosen as therapeutic goals (but nowhere are these group systolic values or statistical analysis provided).
3. Infusions of phenylephrine (100 μg/ml—totaling 960–1,690 μg) versus ephedrine (8 mg/ml—totaling 44.8–79.2 mg) were initiated at 1 ml/min to sustain the therapeutic goal “baseline” pressure.
4. Rescue treatment occurred using phenylephrine 100 μg bolus in both groups without reporting amounts or intervals administered.
5. Supplemental oxygen was withheld unless saturation decreased below 95% (no indication of number of patients given oxygen in any group is provided).
6. The vasopressor was apparently simply “stopped if systolic pressure was greater than 120% baseline,” occurring in approximately 40% of all patients.

We find that
7. While the E versus P group had more hypotension (defined as systolic drop to < 80% of baseline) and phenylephrine rescue (22% vs. 2%), respectively, the mean minimum recorded systolic blood pressures were similar and under classic parameters, not typically requiring treatment in either group (101 vs. 104 Torr, P = 0.33). Eight double the “equipotent volume” of P versus E was infused (13 vs. 7.7 ml), respectively, without information of phenylephrine “rescue” injections/amounts.
8. Hypertension was found in 41% versus 47% of P versus E patients, respectively, and these maximum absolute pressures reported differed significantly statistically (P = 0.044).

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10. Although no information is presented regarding rates of reduction versus termination time intervals of infusions relative to the point of delivery (when calculation of umbilical vein vs. maternal artery levels occurred), strong argumentation is made for ion trapping of ephedrine in the fetus. Consideration of important pharmacokinetic parameters, including α-redistribution phenomena, diffusion gradients of ephedrine present at levels more than 50 times that of phenylephrine, unreported timing of (recent?) phenylephrine bolus doses effecting hemodynamics, and kinetics or interactions of P + E on the resultant fetal blood gases obtained, remains unreported and unknown.

As a clinician, it is interesting that the Apgar score of less than 7 was reported only in a phenylephrine patient (subtle warning?). The use of systolic pressure instead of mean arterial pressure measured by oscillotonometry in awake patients is fraught with motion artifact error. Mean arterial pressure is most reliably detected by this method, and mean blood pressure is perfusion pressure. Defining baseline pressure “on the table” without consideration of clinic outpatient values, failing to prehydrate and continuing vasopressor infusion until pressure exceeds 120% of this most probably relatively hypertensive “defined baseline” value, is clinically questionable. The high rates of hypertension, unusual amounts of pressors administered, and minimum recorded values of 101–104 Torr found in this study and previous studies all reflect variable pressure measured by oscillotonometry in awake patients.

The high rates of hypertension, unusual amounts of pressors administered, and minimum recorded values of 101–104 Torr found in this study and previous studies all reflect variable pressure measured by oscillotonometry in awake patients.

Perhaps, this study simply shows phenylephrine versus ephedrine overtreatment by infusion is easier (but not accurate) to titrate, but is bolus dosing inferior and why? Bolus treatment is certainly more common, typically involves less preparation or total drug injected, may promote more normal pressure, and is effective. Because the blood gas values obtained were within normal limits in both groups, do the statistical differences noted provide any real index of substantial clinical relevance/superiority? Will we ever convert to mean arterial pressure versus systolic pressures in clinical care and investigation? Why not? How does a study of blood pressure and drug dosing/kinetics reach publication, without disclosing absolute values, timing and statistical analysis of the blood pressure, and rescue versus infusion drugs given? Did the 2% and 22% of P versus E group patients, respectively, receive one or multiple doses of rescue phenylephrine and when? Was it the E, or the “P on E” administered in the E group, responsible for the blood gas differences? I look forward to further illumination of this “Holy Grail.” The Burden of Proof has all but been lifted for clinical antihypertensive therapy by this report of hypertensive treatment. Large randomized outcome studies of all complications will be required to prove safety and efficacy of such hypertensive infusion therapy or controlled infusions based in microgram per kilogram per minute and individual responses.

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Possible Influence of Decreasing Maternal Ephedrine Requirements on Fetal/Maternal Concentration Ratio at Delivery

To the Editor:

I read with great interest the article by Ngan Kee et al. It makes a significant contribution to our understanding of the fetal effects of ephedrine during spinal anesthesia for cesarean section. Placental transfer was found to be considerably greater for ephedrine than for phenylephrine, as evidenced by a markedly higher umbilical vein to maternal artery ratio with ephedrine. Interestingly, the umbilical vein to maternal artery ratio was greater than unity for ephedrine, which the authors suggest may have been caused by ion trapping. Could another factor have contributed to this (and to the magnitude of the difference between the groups)? The samples were taken at one point in time (delivery) during a dynamic situation. Ephedrine has a slower onset and a longer duration of action than phenylephrine. During spinal anesthesia for cesarean section, we have observed that ephedrine requirements decrease more rapidly over time than phenylephrine requirements. During the second 15 min after spinal anesthesia, we observed ephedrine requirements decrease more rapidly over time than phenylephrine requirements. The observed differences in neonatal acid–base status demonstrated in many of the studies by Ngan Kee et al. are of unknown clinical significance, but the neonatologists in our center believe that the reported differences are not clinically important. The published normal values for umbilical artery pH after uncomplicated labor and vaginal birth at term are mean pH = 7.28 ± 0.05 (range, 7.15–7.43). Compare those with the values reported in the two studies recently published in Anesthesiology.

1. Phenylephrine is not always effective, and some patients seem to be phenylephrine nonresponders who only get effective response to vasopressor treatment when ephedrine is administered.
2. Phenylephrine can cause bradydysrhythmias that require treatment with atropine. This seems to be more of a problem when an infusion is used.
3. The observed differences in neonatal acid–base status demonstrated in many of the studies by Ngan Kee et al. are of unknown clinical significance, but the neonatologists in our center believe that the reported differences are not clinically important. The published normal values for umbilical artery pH after uncomplicated labor and vaginal birth at term are mean pH = 7.28 ± 0.05 (range, 7.15–7.43). Compare those with the values reported in the two studies recently published in Anesthesiology.
4. One study suggests that Apgar scores are a better measure of neonatal outcome than umbilical cord blood gases. No study that we reviewed on the subject of phenylephrine versus ephedrine for spinal hypotension during CD has been able to show a significant difference in Apgar scores or in neonatal clinical outcome between groups, despite reported differences in umbilical arterial and venous pH.

We would not want to see ephedrine discarded based on the evidence reported to date. Instead, we advocate a common sense approach to the treatment of spinal hypotension during CD. For example, phenylephrine could be used as a first-line treatment, with ephedrine being used either as a second-line treatment or in combination with phenylephrine. Maternal heart rate can be used as a guide to therapy. In addition, it may be prudent to use phenylephrine as the first-line agent in nonelective CD because small differences in fetal pH may have greater effect on clinical neonatal outcome in cases of intrauterine fetal stress. To date, however, studies have failed to show a significant difference in pH or clinical neonatal outcome in this setting, regardless of the vasopressor used.

Ultimately, more research is necessary to look beyond initial umbilical cord blood gas measurements in the delivery room and instead at more long-term neonatal outcomes. This is especially true for cases of CD in which there is suspected fetal compromise. Until

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