be treated with caution.[7] However, randomized controlled trials are not always practical or ethical,[7] 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.[8] 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, $P = 0.33$).
8. Almost double the "equipotent volume" of P *versus* E was infused (13 *vs.* 7.7 ml), respectively, without information of phenylephrine "rescue" injections/amounts.
9. Hypertension was found in 41% *versus* 47% of P *versus* E patients, respectively, and these maximum absolute pressures reported differed significantly statistically ($P = 0.044$).

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 gasses 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 vasopressor overuse rather than any typical clinical care, in which classically 100 Torr or 10–20% drop in systolic pressure from baseline is deemed appropriate in healthy parturients.[3] Is hypertension better than hypotension, to what degree and why? Is this "safe" only in healthy patients, and what is the danger of extrapolation to preeclamptics or others?

The hypertension and lower volume of study infusion administered in the ephedrine group may reflect a specific shortcoming of this indirect acting drug as an infusion candidate *versus* phenylephrine, as indicated previously by Dr. Ngan Kee *et al.*[4] Clinically, bolus dosing of either drug is more typical and prevents inadvertent overinfusions. The higher absolute milligram dose per milliliter of ephedrine infusate may have facilitated diffusion across the placental gradient during administration, whereas the lower total volume administered suggests that a tapering (termination) occurred relative to the time of delivery at 27 min; only 7.7 ml (mean) was infused *versus* the baseline rate of 1.0 ml/min, which would have yielded 27 ml at delivery. The high umbilical vein/maternal artery ratio found may reflect simple reverse fetal-to-maternal diffusion kinetics of previously higher fetal (and maternal) ephedrine levels into the hyperdynamic mother's circulation (after infusion termination) of a drug with 3- to 5-h renal elimination $T_{1/2}$ and a volume of distribution of 3 l/kg (*i.e.*, standard uptake and elimination kinetics).* What were the time intervals from ephedrine/P infusion termination and rates relative to the umbilical vein/maternal artery blood level ratios in individual patients and in different groups? Was typically *P* infused/bolus injected up to delivery, thus maintaining the maternal-to-fetal gradient of diffusion found?

Dr. Smiley suggests that this study is further proof of clinical superiority of phenylephrine, and possibly infusion over bolus therapy, perhaps as a "believer" of this Holy Grail. I question this "proof" itself, validity, and values of baseline definitions: What blood pressure was the "desired baseline" and is it appropriate for these two groups from a Chinese population, known to exhibit lower pressures than Americans by diet and predisposition, a baseline determined other than from standard unstressed clinical method? Where is the missing data: no mention of herbal medical treatment as exclusion factor in this Chinese population with "traditional medicine" (*i.e.*, not Western traditional medicine) trend toward such use, which may have effected ephedrine responses/kinetics, the fact that "equipotent" phenylephrine was apparently infused more continually/longer/later, and what amounts of crystalloid infusion and rescue drug/patient/per group and the relative interval time of last dose to delivery of any/all drugs were administered?

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 antihypotensive 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.*[1] 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.[2] During the second 15 min after spinal anesthesia, we observed ephedrine requirements to be 26% of those in the first 15 min compared with 79% for phenylephrine. If maternal ephedrine concentration was decreasing before delivery, this may have decreased, or even caused a reversal in, the maternal/fetal concentration gradient for ephedrine at the time of delivery.

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Ephedrine and Phenylephrine Use during Cesarean Delivery

To the Editor:

We read with interest the articles by Ngan Kee *et al.*[1] and Dyer *et al.*,[2] as well as the editorial by Smiley,[3] all of which concern comparisons of phenylephrine and ephedrine for the treatment of hypotension associated with spinal anesthesia for cesarean delivery (CD). It is reassuring to know that phenylephrine can be used safely in this setting, something that I (D.R.G.) have advocated to residents and colleagues for more than 10 yr. However, it is important to remember that ephedrine too has been used safely for decades to treat hypotension after induction of spinal anesthesia for CD. Therefore, it is crucial that the results of these recent studies are put into perspective and do not lead to an imposed or voluntary discontinuation of ephedrine use during CD. The reasons for this are as follows:

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).[4] Compare those with the values reported in the two studies recently published in ANESTHESIOLOGY[1,2] (table 1).
4. One study suggests that Apgar scores are a better measure of neonatal outcome than umbilical cord blood gases.[5] 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.[6–13]

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.[10]

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