

Burden of Proof

IN early 2009, a 2-day symposium on Obstetric Anesthesia had just ended and my colleague and I stepped onto the tram in Basel, Switzerland, to begin our respective journeys home. One of the final discussions at the conference had concerned treatment/prevention of hypotension during spinal anesthesia for Cesarean delivery. I had spoken about the evidence in favor of phenylephrine infusions, and my personal practices in using the drug. On the tram, I asked my colleague what he generally used to treat hypotension during Cesareans and he responded "Boluses of ephedrine or phenylephrine, as does most of the rest of my group." The following month, as I began a lecture at a continuing medical education course, I asked the audience, composed of a mixture of anesthesiologists and certified registered nurse anesthetists (CRNAs), "What is your first-line drug to treat hypotension at Cesarean section, ephedrine or phenylephrine?" Ninety percent responded ephedrine. The next week, one of our current departmental Fellows, who had done his residency in our institution and was quite familiar with both the evidence for and our practice in using phenylephrine infusions and who was about to sit for his oral American Board of Anesthesiologists examination, asked me, "What do I say if they ask me what drug I would use for hypotension during Cesarean section? Is phenylephrine an acceptable answer?" The response from the audience of predominantly nonobstetric anesthesia providers is perhaps not so shocking, despite the fact that there exists over a decade of fairly consistent evidence from well-designed, randomized, blinded studies in Europe,[1,2] the United States,[3–5] and Asia[6,7] supporting the proposition that phenylephrine is at least as safe and effective and probably preferable to ephedrine for the treatment or prevention of hypotension at Cesarean section. Not every anesthesiologist or CRNA reads every journal, interprets evidence correctly, is willing to change his or her practice on the basis of the available information, or even believes in the principle of evidence-based practice. The question from the Fellow reflects the fear and insecurity that all of us felt as we approached our oral exam, even when we thought we knew the answer to a clinical question. We wondered what those Board examiners knew (or didn't know) and what they would accept as answers. The comments of my colleague on the tram, however, were a bit more surprising, as they came from the Editor-in-Chief of this Journal, whose clinical practice is and has been predominantly in obstetric anesthesia. A few weeks later, Dr. Eisenach emailed me to tell me that he had started using phenylephrine infusions, had convinced several colleagues at his institution to also do so, and invited me to write this editorial.

In this issue of Anesthesiology, Ngan Kee *et al.* report on a blinded, randomized clinical trial comparing phenylephrine infusion to ephedrine infusion for the prevention and treatment of hypotension at Cesarean section under spinal anesthesia.[8] The question of how to prevent or treat hypotension during spinal anesthesia for Cesarean section has been a central question in obstetric anesthesia for decades. The answer has been called the Holy Grail of obstetric anesthesia.[9] For decades ephedrine was the drug of choice, based on classic studies in sheep that suggested deleterious effects of pure α-adrenergic agonists on uteroplacental blood flow.[10] Multiple reports in the 1990s and early 21st century, many by Dr. Ngan Kee and his colleagues in Hong Kong,[1,3–6,11–14] have demonstrated that phenylephrine or other α-agonists (*e.g.*, metaraminol) are safe and generally more effective than ephedrine at preventing maternal hypotension and its symptoms (*e.g.*, nausea and vomiting). In addition, it has become clear that ephedrine use often leads to lower neonatal pH and a higher incidence of neonatal acidosis than does the use of phenylephrine or other pure α-agonists. The cause of this relative acidosis has been postulated not to be directly related to uteroplacental blood flow (fetal asphyxia) but rather to the effect of ephedrine as a metabolic stimulant within the fetus, resulting in a relatively hypermetabolic state. Indirect evidence for this theory was provided in a variety of ways: umbilical artery-vein differences, the dependence on ephedrine dose, and the lack of observable differences in uteroplacental perfusion that could otherwise explain a deleterious effect of ephedrine on neonatal pH or base excess.[2,15]

In the current study, Ngan Kee *et al.* randomly assigned 104 patients undergoing elective Cesarean section with spinal anesthesia to groups receiving infusions of either ephedrine (8 mg/ml) or phenylephrine (100 μg/ml), titrated to maintain baseline preoperative systolic blood pressure. Blood pressure was better maintained in the phenylephrine group, with fewer episodes of hypotension and need for rescue boluses. Umbilical arterial pH was lower in the ephedrine group (7.25 *vs.* 7.33), with higher P_{CO_2} (56 mmHg *vs.* 49 mmHg) and a more negative base excess (−4.8 *vs.* −1.9). Maternal side effects were decreased with phenylephrine, with an incidence

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of nausea or vomiting of 35% in the ephedrine group *versus* 2% (1 patient) with phenyephrine. Concentrations of glucose, lactate, epinephrine, and norepinephrine were significantly higher in the umbilical blood of the ephedrine group. Most importantly, for the first time in studies comparing ephedrine and phenylephrine, the investigators measured maternal and umbilical arterial and venous phenylephrine and ephedrine concentrations. Fetal:maternal ratios of ephedrine were significantly higher than those for phenylephrine, with umbilical concentrations of phenylephrine 10–20% of maternal, whereas ephedrine concentrations were comparable to maternal concentrations. These findings confirm the previously held suspicion that ephedrine crosses the placenta more readily than phenylephrine and support the concept that an increase in fetal metabolism caused by ephedrine is the cause of the increase in base deficit and increase in other markers of fetal metabolic stress.

The current study is well-done, the results are almost certainly valid, and perhaps more importantly, it is consistent with almost every study done over the past 15 yr comparing the two interventions at comparable doses. What are we then to make of the fact that practice, even that of very well-informed anesthesiologists, does not seem to have changed in response to the evidence? If the Holy Grail has been found and is readily accessible, why are so few celebrating or drinking from it?

Several explanations suggest themselves. First, we should not be so quick to change long-accepted practices based on one (or two or perhaps three) studies. The "burden of proof" should be on the new therapy, especially when conventional therapy is reasonably effective and reasonably safe, as is the case with ephedrine boluses or infusions. Indeed, recent experience with perioperative β-adrenergic antagonist recommendations and some studies of tight glucose control suggest that clinicians should be appropriately wary of following every new evidenced-based trend. As many have learned in a different context, a buy-and-hold strategy may frequently be superior to a day-trader approach in which a clinician attempts to adopt every new trend and piece of evidence that presents itself, especially in a "safety-first" subspecialty such as obstetric anesthesiology that deals with a predominantly healthy population. Second, the phenylephrine *versus* ephedrine issue is perceived as not being quite a life and death issue. The pH and base deficit differences are consistent and statistically significant in most studies, but they are not all that dramatic, typically a pH difference of 0.02 or 0.05. Thus, many clinicians may just not think it worth their while to learn a new strategy. Third, setting up an infusion, the preferred method of administering phenylephrine (and probably ephedrine) based on the evidence, is a bit more time consuming than simply injecting boluses from a syringe. Fourth, some clinicians, even some who would concede the evidence in favor of phenylephrine for routine elective Cesarean delivery, may argue that the safety and superiority of α-agonist vasopressor treatment has not been demonstrated in parturients with severe preeclampsia or other scenarios with significantly decreased uteroplacental flow and/or increased resistance, and more work in this area is both needed and ongoing.[16,17] Fifth, it must be acknowledged that much of the work demonstrating the efficacy or superiority of phenylephrine comes from the Ngan Kee group, and confirmation from other centers and investigators should be required before widespread acceptance of any clinical recommendation. However, studies elsewhere have confirmed the major findings.[1–5,13] Finally, of course, there are those who still do not quite believe the evidence is convincing.[18]

However, thanks in large part to the consistent, high-quality, and productive clinical investigations of Ngan Kee and colleagues in Hong Kong, the evidence now is sufficient for a change in attitude and practice to be strongly encouraged. The weight of the evidence has now equaled the burden of proof, and our clinical burden should be to incorporate the evidence into our routine practice. This recommendation is finding its way into review articles from a variety of countries.[19–22] Titrated phenylephrine infusions minimize maternal nausea, vomiting, and episodes of hypotension, and they result in higher neonatal pH and lower base deficits. A variety of specific dosing strategies can be used and have been published,[2,6,23,24] but doses in the range of 25–100 μg/min titrated to maintain maternal blood pressure near baseline values appears to be very effective and relatively easy to employ. It is the therapeutic strategy that most anesthesiologists would want for themselves or family members as patients, and it should probably be the default choice for prevention and treatment of hypotension during spinal anesthesia for elective Cesarean delivery in the absence of a specific contravening rationale or contraindication. As the famous Alka-Seltzer ad from the 1970s said, "Try it, you'll like it," and so will your patients.

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Placental Transfer and Fetal Metabolic Effects of Phenylephrine and Ephedrine during Spinal Anesthesia for Cesarean Delivery

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Background: **Use of ephedrine in obstetric patients is associated with depression of fetal acid-base status. The authors hypothesized that the mechanism underlying this is transfer of ephedrine across the placenta and stimulation of metabolism in the fetus.**

Methods: **A total of 104 women having elective Cesarean delivery under spinal anesthesia randomly received infusion of phenylephrine (100 μg/ml) or ephedrine (8 mg/ml) titrated to maintain systolic blood pressure near baseline. At delivery, maternal arterial, umbilical arterial, and umbilical venous blood samples were taken for measurement of blood gases and plasma concentrations of phenylephrine, ephedrine, lactate, glucose, epinephrine, and norepinephrine.**

Results: **In the ephedrine group, umbilical arterial and umbilical venous pH and base excess were lower, whereas umbilical arterial and umbilical venous plasma concentrations of lactate, glucose, epinephrine, and norepinephrine were greater. Umbilical arterial P_{CO_2} and umbilical venous P_{O_2} were greater in the ephedrine group. Placental transfer was greater for ephedrine (median umbilical venous/maternal arterial plasma concentration ratio 1.13 *vs.* 0.17). The umbilical arterial/umbilical venous plasma concentration ratio was greater for ephedrine (median 0.83 *vs.* 0.71).**

Conclusions: **Ephedrine crosses the placenta to a greater extent and undergoes less early metabolism and/or redistribution in the fetus compared with phenylephrine. The associated increased fetal concentrations of lactate, glucose, and catecholamines support the hypothesis that depression of fetal pH and base excess with ephedrine is related to metabolic effects secondary to stimulation of fetal β-adrenergic receptors. Despite historical evidence suggesting uteroplacental blood flow may be better maintained with ephedrine, the overall effect of the vasopressors on fetal oxygen supply and demand balance may favor phenylephrine.**

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REGIONAL anesthesia is normally preferred for Cesarean delivery because it avoids the maternal risks of general anesthesia such as aspiration of gastric contents and difficulty with airway management.[1] Although it is generally accepted that regional anesthesia confers greater safety for the mother compared with general anesthesia, its effects on neonatal outcome are controversial, particularly for spinal anesthesia. For example, several studies have shown that the risk of fetal acidosis is greater with spinal anesthesia compared with general anesthesia,[2] and a recent large retrospective study has found that neonatal mortality of very preterm infants born by Cesarean delivery under spinal anesthesia was greater than that of comparable infants delivered under general anesthesia.[3] The mechanism underlying these observations is uncertain, but recent data suggest that an important contributing factor may be the widespread use of ephedrine to treat and prevent hypotension during regional anesthesia.[4,5] Historically, ephedrine was recommended as the vasopressor of choice in obstetrics but there is now increasing evidence that ephedrine has the propensity to decrease fetal pH and base excess, especially in comparison with other vasopressors such as phenylephrine[4,6] and metaraminol.[7]

The reason why ephedrine is associated with fetal acidosis is unknown. The original recommendations in favor of ephedrine were based on animal and *in vitro* data that showed that ephedrine has lesser propensity to cause vasoconstriction of the uteroplacental circulation compared with α-adrenergic agonists.[8] Little regard was given to the possibility that vasopressors may have direct effects on the fetus. Recently, however, it has been postulated that a mechanism explaining the acid-base changes associated with ephedrine is stimulation of fetal metabolism after placental transfer of ephedrine and stimulation of fetal β-adrenergic receptors.[5,6] However, there are few experimental data available on comparative placental transfer of vasopressors and little information to support this hypothesis. Therefore, we designed this randomized, double-blind study to quantify and compare placental transfer of ephedrine and phenylephrine and the effect of these vasopressors on a number of biochemical markers of metabolism in mother and newborn when used to maintain blood pressure during spinal anesthesia for elective Cesarean delivery.

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Materials and Methods

The study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee, Shatin, Hong Kong, China, and was registered in the Centre for Clinical Trials Clinical Registry of the Chinese University of Hong Kong (unique trial number CUHK_CCT00079). All patients gave written informed consent. We recruited 104 American Society of Anesthesiologists physical status 1 and 2 women with term singleton pregnancies scheduled for elective Cesarean delivery under spinal anesthesia. Exclusion criteria were hypertension (systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg), cardiovascular or cerebrovascular disease, known fetal abnormality, contraindications to spinal anesthesia, and signs of onset of labor.

Patients received oral famotidine and sodium citrate as premedication. On arrival to the operating room, standard noninvasive monitoring was applied, and patients were positioned in the left-tilted supine position for several minutes, during which blood pressure was measured every 1–2 min. Blood pressure measurements were continued until they became consistent (three successive measurements of systolic blood pressure that had a difference of no more than 10%). Baseline systolic blood pressure and heart rate were calculated as the mean of the three recordings.

A 16-gauge IV cannula was then inserted into a forearm vein under local anesthesia and connected by using a wide-bore infusion set to a 1-l bag of warmed lactated Ringer's solution. No intravenous prehydration was given. Spinal anesthesia was induced in the right lateral position. After skin infiltration with lidocaine, a 25-gauge pencil-point needle was inserted at what was estimated to be the L3-4 or L4-5 vertebral interspace and 2.0 ml of hyperbaric 0.5% bupivacaine (10 mg) and 15 μg of fentanyl were injected intrathecally. The patient was then returned to the left-tilted supine position. Blood pressure was measured at 1-min intervals beginning 1 min after spinal injection. Hemodynamic data were downloaded to a computer at 5-s intervals.

Patients were randomly allocated to have their blood pressure maintained using an infusion of either phenylephrine 100 μg/ml (phenylephrine group) or ephedrine 8 mg/ml (ephedrine group) by drawing of sequentially numbered sealed envelopes that each contained a computer-generated randomization code (Statview for Windows 5.0.1; SAS Institute Inc, Cary, NC). Replacement randomization was used when the codes were generated to ensure equal numbers in each group.[9] To facilitate double-blinding, the drugs were prepared in identical syringes by one of the investigators who was not involved with subsequent patient management or data collection. The concentrations of vasopressors were chosen on the basis of previously published estimates of comparative potency.[10] The vasopressors were infused by using a syringe pump (Graseby 3500 Anaesthesia Pump; Graseby Medical Ltd., Watford, Herts, United Kingdom) that was connected *via* fine-bore tubing to the IV cannula by using a 3-way stopcock. Infusion rates were adjusted to maintain systolic blood pressure near to baseline values by using a previously described regimen.[11,12] At intrathecal injection, rapid IV fluid infusion (maximum 2 l) was started by fully opening the valve of the infusion set with the fluid bag suspended 1.5 m above the operating table, and the vasopressor was commenced at 60 ml/h. For 2 min, the infusion was continued unless systolic blood pressure was more than 120% of baseline. Subsequently, until terminating the study at uterine incision, systolic blood pressure was measured every 1 min, and the infusion was continued if systolic blood pressure was less than or equal to baseline and stopped if systolic blood pressure was greater than baseline. If there were more than two consecutive episodes of hypotension (defined as systolic blood pressure less than 80% of baseline) a "rescue" IV bolus of 100 μg of phenylephrine was given. The incidence of hypertension, defined as systolic blood pressure greater than 120% of baseline, was recorded.

Five minutes after intrathecal injection, the upper sensory level of anesthesia was recorded by assessing loss of pinprick discrimination, and the surgeon was invited to scrub. Further checks of the block height were made as required before the start of surgery, but these levels were not recorded as part of the study. Surgical times and the incidences of nausea or vomiting were recorded. Supplemental oxygen was not given unless arterial oxyhemoglobin saturation was less than 95%. Bradycardia (heart rate less than 50 beats/min) was treated by stopping the vasopressor and, if accompanied by hypotension, with 0.6 mg of IV atropine.

At the time of delivery, a 5- to 10-ml sample of maternal arterial (MA) blood was taken with a heparinized syringe by radial artery puncture. Immediately after delivery, samples of umbilical arterial (UA) and umbilical venous (UV) blood were taken from a double-clamped segment of cord. With these samples, the following measurements were made: (1) blood gases by using a Rapid Point 400 analyzer (Bayer Diagnostics Mfg [Sudbury] Ltd., Sudbury, United Kingdom); (2) plasma concentrations of lactate and glucose by using the Vitros DT60 II Chemistry System (Ortho-Clinical Diagnostics, Raritan, NJ); (3) plasma concentrations of epinephrine and norepinephrine by using methods described in appendix 1; (4) plasma concentrations of phenylephrine or ephedrine by using methods described in appendix 2.

After delivery, Apgar scores were assessed 1 and 5 min by the attending pediatrician.

Statistical Analysis

No preliminary data for umbilical arterial or venous concentrations of vasopressors were available, so sample

Table 1. Patient Characteristics and Surgical Times

	Phenylephrine Group (n = 52)	Ephedrine Group (n = 52)	*P* Value
Age, yr	32 (4.7)	32 (4.7)	0.58
Weight, kg	70 (15.7)	70 (10.5)	0.94
Height, cm	156 (5.3)	157 (4.9)	0.24
Block height, dermatome	T6 [T4–T7]	T4.5 [T3–T6]	0.14
Induction-to-delivery interval, min	27.6 [22.3–30.9]	27.6 [23.0–31.9]	0.93
Incision-to-delivery interval, min	7.3 [5.2–11.2]	7.3 [5.4–11.3]	0.92
Uterine incision-to-delivery interval, s	88 [60–119]	87 [60–125]	0.34

Values are mean (standard deviation) or median [interquartile range].

size calculation was based on potential differences in UA pH. Assuming SD of 0.04[12] and anticipated difference of 0.03,[4] we calculated that a sample size of 38 patients per group would be required to have 90% power with a two-sided α value of 0.05. However, in anticipation from previous experience that obtaining sufficient maternal arterial and umbilical cord blood would likely be difficult in a proportion of cases, the sample size was arbitrarily increased by one-third to give a final sample size of 52 patients per group. Patient characteristics were compared by using Student *t* test. Other data were compared using the Mann–Whitney U test for unpaired data, the Wilcoxon signed-ranks test for paired data, and the chi-square test or Fishers' exact test for categorical data. $P < 0.05$ were considered significant. All analyses were performed using SPSS 15.0.1.1 (SPSS Inc., Chicago, IL).

Results

All 104 patients completed the study. Insufficient blood was obtained from varying numbers of patients in each group for the different assays, as indicated in the tables. Hemodynamic data were excluded from analysis from one patient in each group because severe shivering caused measurement artifacts.

There was no difference between groups in patient characteristics (table 1). Results of analysis of blood gases are shown in table 2. UA and UV pH and base excess were lower in the ephedrine group compared with the phenylephrine group. UA Pco_2 and UV Po_2 were greater in the ephedrine group compared with the phenylephrine group.

Plasma concentrations of lactate, glucose, epinephrine, norepinephrine, phenylephrine, and ephedrine are shown in table 3. The plasma concentration of epinephrine was below the lower limit of detection (20 pg/ml) in 16 MA and three UV samples in the ephedrine group and seven MA samples in the phenylephrine group; for the purpose of analysis, each of these results was assigned a value of 19 pg/ml. UA and UV plasma concentrations of lactate, glucose, epinephrine, and norepinephrine were all greater in the ephedrine group compared with the phenylephrine group. MA plasma concentrations of glucose, epinephrine, and norepinephrine were all greater in the ephedrine group compared with the phenylephrine group. UV/MA and UA/UV plasma concentration ratios for phenylephrine and ephedrine are shown in figure 1. For the ephedrine group *versus* the phenylephrine group, the UV/MA ratio was greater (median 1.13 [interquartile range 1.01–1.23] *vs.* 0.17 [0.11–0.22], $P < 0.001$) and the UA/UV ratio was greater (0.83 [0.75–0.91] *vs.* 0.71 [0.56–0.84], $P = 0.001$).

Birthweight and Apgar scores were similar between groups. One neonate in the phenylephrine group had an Apgar score of 6 at 1 min; all other scores at 1 min and 5 min were 7 or greater.

Table 2. Blood Gases

	Phenylephrine Group	Ephedrine Group	*P* Value
Maternal arterial			
Number of samples	45	45	
pH	7.42 [7.41 to 7.44]	7.42 [7.41 to 7.43]	0.14
Pco_2, mmHg	33 [30 to 35]	34 [32 to 36]	0.15
Po_2, mmHg	111 [101 to 123]	112 [99 to 122]	0.68
Base excess, mmol/l	–2.3 [–2.9 to –1.5]	–2.3 [–3.1 to –1.3]	0.98
Umbilical arterial			
Number of samples	51	51	
pH	7.33 [7.30 to 7.35]	7.25 [7.14 to 7.29]	<0.001
Pco_2, mmHg	49 [42 to 54]	56 [48 to 66]	<0.001
Po_2, mmHg	20 [18 to 22]	20 [17 to 24]	0.57
Base excess, mmol/l	–1.9 [–3.2 to –0.6]	–4.8 [–8.7 to –3.0]	<0.001
Umbilical venous			
Number of samples	49	52	
pH	7.34 [7.33 to 7.35]	7.31 [7.26 to 7.34]	<0.001
Pco_2, mmHg	46 [43 to 49]	47 [42 to 51]	0.49
Po_2, mmHg	28 [25 to 32]	30 [27 to 33]	0.03
Base excess, mmol/l	–1.6 [–2.4 to –0.7]	–4.3 [–6.2 to –2.6]	<0.001

Values are number or median [interquartile range].

Table 3. Plasma Concentrations of Lactate, Glucose, Epinephrine, Norepinephrine, Phenylephrine, and Ephedrine

	Phenylephrine Group	Ephedrine Group	*P* Value
Maternal arterial			
Lactate, mmol/l	2.3 [2.0–2.7] (44)	2.4 [2.0–2.7] (45)	0.56
Glucose, mg/dl	80 [76–85] (44)	86 [80–94] (45)	0.003
Epinephrine, pg/ml	33.5 [19–54] (46)	47 [22–73] (50)	0.046
Norepinephrine, pg/ml	115 [92–178] (45)	297 [223–390] (50)	<0.001
Phenylephrine, ng/ml	8.2 [5.7–10.7] (47)		
Ephedrine, ng/ml		366.5 [306.5–523.5] (50)	
Umbilical arterial			
Lactate, mmol/l	2.2 [1.9–2.6] (52)	4.2 [3.0–6.7] (49)	<0.001
Glucose, mg/dl	55 [49–60] (52)	63 [59–71] (49)	<0.001
Epinephrine, pg/ml	525 [289–852] (45)	696 [507–1,291] (49)	0.019
Norepinephrine, pg/ml	2,158 [1,526–3,403] (46)	5,523 [3,066–9,538] (49)	<0.001
Phenylephrine, ng/ml	0.9 [0.6–1.2] (47)		
Ephedrine, ng/ml		355.2 [254.5–545.2] (47)	
Umbilical venous			
Lactate, mmol/l	2.2 [1.9–2.4] (51)	3.4 [2.7–5.1] (50)	<0.001
Glucose, mg/dl	66 [61–70] (51)	73 [68–79] (50)	<0.001
Epinephrine, pg/ml	97 [50–214] (50)	132 [84–226] (52)	0.039
Norepinephrine, pg/ml	446 [293–683] (50)	1,568 [812–2,940] (52)	<0.001
Phenylephrine, ng/ml	1.4 [0.8–1.9] (47)		
Ephedrine, ng/ml		434.5 [334.0–594.3] (52)	

Values are number or median [interquartile range] (number of samples).

Hemodynamic changes, vasopressor use, and the incidence of nausea and vomiting are summarized in table 4. Patients in the ephedrine group received a smaller volume of vasopressor but had higher incidences of hypotension and nausea/vomiting and required more rescue does of phenylephrine. The maximum recorded systolic blood pressure was greater in the ephedrine group, but the minimum recorded heart rate was lower and the incidence of bradycardia was greater in the phenylephrine group. No patient required atropine or supplemental oxygen.

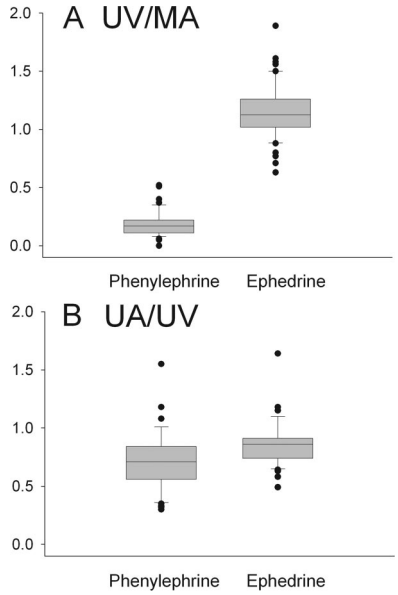

Fig. 1. Plasma concentration ratios for phenylephrine and ephedrine. Data are shown for (*A*) umbilical venous to maternal arterial (UV/MA) and (*B*) umbilical arterial to umbilical venous (UA/UV) ratios. *Box plots* display the 25th, 50th, and 75th percentiles as *horizontal lines* on a bar, *whiskers* above and below the box indicate the 90th and 10th percentiles, and data beyond the 10th and 90th percentiles are displayed as individual *points*. Data were significantly different between groups ($P \leq 0.001$) for both concentration ratios.

Discussion

Our study showed that ephedrine crosses the placenta to a greater extent than phenylephrine, as evidenced by considerably greater values for UV/MA plasma concentration ratios in the ephedrine group. Furthermore, the UA/UV plasma concentration ratios were also greater in the ephedrine group, which suggests that ephedrine undergoes early metabolism and/or redistribution in the fetus to a lesser extent compared with phenylephrine. Our results confirmed the results of previous studies that have shown that use of ephedrine is associated with lower values for fetal pH and base excess compared with phenylephrine.[4,6] In addition, we found that use of ephedrine was associated with greater UA and UV plasma concentrations of lactate, glucose, epinephrine, and norepinephrine and greater UV P_{CO_2} compared with phenylephrine. Together, these findings are consistent with the hypothesis that the mechanism underlying the propensity for ephedrine to cause fetal acidosis is transfer of the drug across the placenta and stimulation of metabolic processes in the fetus.

Early studies of vasopressors in obstetrics focused mainly on differences among agents in their effect on uteroplacental blood flow. Animal studies showed that the latter was better maintained with ephedrine compared with α-agonists,[8] which led to the clinical recommendation that ephedrine should be the vasopressor of

Table 4. Hemodynamic Changes, Intravenous Fluid, and Vasopressor Consumption

	Phenylephrine Group	Ephedrine Group	*P* Value
Total volume of vasopressor given, ml	13 [9.6–16.9]	7.7 [5.6–9.9]	<0.001
Total intravenous fluid, ml	1,725 [1,200–2,010]	1,800 [1,450–2,010]	0.36
Incidence of hypotension	2 (4%)	13 (25%)	0.002
Minimum recorded systolic blood pressure, mmHg	104 [96–109]	101 [87–108]	0.33
Rescue phenylephrine required	1 (2%)	11 (22%)	0.002
Incidence of hypertension	21 (41%)	24 (47%)	0.55
Maximum recorded systolic blood pressure, mmHg	134 [127–140]	139 [129–152]	0.044
Incidence of bradycardia (heart rate < 50 beats/min)	6 (12%)	0 (0%)	0.03
Minimum recorded heart rate, beats/min	58 [54–65]	70 [63–78]	<0.001
Nausea or vomiting	1 (2%)	18 (35%)	<0.001

Values are median [interquartile range] or number (%).

choice in obstetric anesthesia because greater uteroplacental blood flow should correspond to greater oxygen supply to the fetus. However, recent clinical data showing that the use of ephedrine is in fact associated with lower values for fetal pH and base excess has led to the reevaluation of older teaching. These data together with the results of our current study suggest that it is also important to consider oxygen demand of the fetus; the most important factor affecting short-term fetal acid-base status is probably the balance between fetal oxygen supply and demand. Although ephedrine may have more favorable effects on fetal oxygen supply compared with phenylephrine, this advantage may be negated by its greater placental transfer and the undesirable effects of this on fetal oxygen demand. When comparing the net effect of vasopressors on fetal oxygen supply and demand balance, we believe that currently available data favor the choice of phenylephrine.

In the current study, UV Po_2 was lower in the phenylephrine group compared with the ephedrine group, which is similar to findings from our other recent studies.[13,14] The exact mechanism underlying this observation is uncertain, but a possible explanation is that it may reflect the greater vasoconstrictive effect of phenylephrine on the uteroplacental circulation. Studies in sheep have shown that, although uterine blood flow varies over a wide range, fetal oxygen uptake remains relatively constant, suggesting that the efficiency of oxygen extraction by the fetus is increased when uteroplacental perfusion decreases.[15] If the same mechanism is present in humans, a reduction of uteroplacental perfusion caused by phenylephrine with an associated increase in fetal oxygen extraction per unit of uteroplacental blood flow would result in decreased uterine venous Po_2 and thus decreased umbilical venous Po_2 because the human placental is considered to function as a venous equilibrator. Under normal clinical conditions, any potential adverse effects of phenylephrine on uteroplacental blood flow do not appear to be detrimental because fetal acidosis is not observed with usual clinical doses of phenylephrine. This is consistent with animal studies that have demonstrated that, under normal physiologic conditions, uterine blood flow is in excess of the minimum required to satisfy fetal oxygen demand,[16] which confers a margin of safety that, to a degree, protects the fetus from fluctuations in uterine blood flow.[17] However, it is possible that this may not apply in the presence of acute or chronic uteroplacental insufficiency. Therefore, some caution may be prudent when using large doses of phenylephrine in the presence of clinical evidence of fetal compromise, although in a recent comparison of ephedrine and phenylephrine in nonelective Cesarean delivery, we did not find that use of moderate doses of phenylephrine (median dose before delivery, 100 μg; range 0–1,200 μg) to be associated with any evidence of detrimental effects on the fetus.[14]

The greater placental transfer of ephedrine compared with phenylephrine can be explained by consideration of differences in the molecular structures of these drugs. Both ephedrine and phenylephrine are structurally related derivatives of phenylethylamine. However, unlike phenylephrine, ephedrine lacks hydroxy-substitution of the aromatic ring; in addition, it has an α-methyl substitution of the ethyl sidechain, which phenylephrine lacks. Thus ephedrine can be expected to have greater lipid solubility than phenylephrine, which explains its greater placental transfer. Ephedrine also crosses the blood brain barrier and has central stimulant and appetite suppressant effects.[18] Of note, our results showed that the median UV/MA plasma concentration ratio for ephedrine was greater than unity, indicating that not only did ephedrine readily cross the placenta; in most patients, UV plasma concentrations were even greater than MA concentrations. This may be the result of ion trapping, which may occur when ephedrine, a basic drug (pKa 9.6), becomes more protonated (ionized) when exposed to the lower pH environment of the fetus, analogous to the effect observed for local anesthetics.[19] This effect may be accentuated as fetal pH decreases secondary to ephedrine's metabolic effects.

The metabolic effects of ephedrine on the fetus can be explained by the fact that, in contrast to phenylephrine, ephedrine has significant β adrenoceptor activity.[20] β stimulation has previously been shown to stimulate me-

tabolism in fetal lambs after isoproterenol administration and in human neonates after administration of terbutaline before Cesarean delivery.[21] As a result of its indirect action, ephedrine stimulates presynaptic release of norepinephrine, which likely contributed to the higher circulating plasma concentrations of norepinephrine in umbilical blood in the ephedrine group. We also observed maternal effects of ephedrine as evidenced by greater MA plasma concentrations of glucose, epinephrine, and norepinephrine in the ephedrine group.

The ratio of phenylephrine:ephedrine concentrations in the solutions we used assumed a potency ratio of 80:1 as reported by Saravanan *et al.*[10] However, patients in the ephedrine group received a smaller total volume of vasopressor compared with the phenylephrine group, which suggests that the actual potency ratio may be lower. Although patients in the ephedrine group had a greater incidence of hypotension and required more rescue doses of phenylephrine, there was no difference between groups in the minimum recorded systolic blood pressure although maximum recorded systolic blood pressure was greater in the ephedrine group. These varying results illustrate the difficulty in comparing potencies of two drugs that differ in speed of onset and duration of action.

Although the current study and other recent clinical studies have demonstrated that ephedrine is associated with a greater propensity toward fetal acidosis compared with phenylephrine[4,6] and other α-agonists,[7] it is uncertain whether this has potential to affect clinical outcome. It should be noted that the majority of published comparative studies, including the current study, have been performed in low-risk elective cases when small differences in anesthetic technique are unlikely to have a major effect on neonatal outcome. It is possible that the metabolic effects of ephedrine on the fetus may be more important in the presence of other factors that may affect the fetal oxygen supply:demand balance, although we found no difference in outcome in our previous study of nonelective Cesarean deliveries.[14] Of note, a secondary analysis of the large retrospective EPIPAGE study found that neonatal mortality of very preterm infants born by Cesarean delivery under spinal anesthesia was greater than that of comparable infants delivered under general anesthesia (adjusted odds ratio 1.7, 95% confidence interval 1.1 to 2.6) after adjustment for confounding variables, including gestational age and characteristics of the mother, pregnancy, delivery, neonate, and medical management.[3] The exact mechanism for this finding is uncertain, but severe or sustained hypotension and excessive use of ephedrine were suggested as possible contributing factors. Further work, ideally from prospective studies, is required to confirm these findings.

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Appendix 1: Method Used to Measure Plasma Concentrations of Epinephrine and Norepinephrine

Blood samples were collected and transferred into lithium heparin tubes containing dilute sodium metabisulfite as an antioxidant and were placed in ice. Samples were immediately centrifuged at 4°C, and the plasma was separated and stored at −80°C pending batch analysis. Norepinephrine and epinephrine were measured by using high-perfor-

mance liquid chromatography with electrochemical detection. The catecholamines were isolated by using alumina adsorption under basic conditions and then reextracted from the alumina using dilute acid solution before their analysis on the high-performance liquid chromatography with electrochemical detection system. The analytes were separated on a reversed-phased column (Ultrasphere intraperitoneal; C18, Beckman Instruments Inc., Fullerton, CA) by using a mobile phase containing methanol-citric acid-EDTA-octane sulfonic acid-water under isocratic condition. Quantitation was then performed by monitoring the drugs by electrochemical detection using a coulometric detector (ESA 5100A; Environmental Science Associates, Bedford, MA). The assay was linear to the lower limit of detection (25 pg/ml for both epinephrine and norepinephrine). There were good linear responses for both epinephrine and norepinephrine, with correlation coefficients better than 0.9980. The lowest limit of detection was at 25 pg/ml at a signal-to-noise ratio of 3. The within-day coefficients of variation for epinephrine and norepinephrine ranged from 5.52% to 10.62% (mean 8.55%) and 2.53% to 10.57% (mean 6.93%), respectively. The between-day coefficients of variation were 6.49% to 10.07% (mean 8.18%) and 7.33% to 13.02% (mean 10.29%), respectively.

Appendix 2: Method Used to Measure Plasma Concentrations of Phenylephrine and Ephedrine

A sensitive method was developed for the analysis of phenylephrine and ephedrine in plasma by using high-performance liquid chromatography-tandem mass spectrometry. Blood samples were collected into heparinized tubes containing sodium metabisulfite as preservative. The tubes were placed in ice, and the blood samples were immediately centrifuged at 4°C. Plasma was collected and stored at −80°C pending batch analysis. A volume of 0.5 ml of plasma was used for both phenylephrine and ephedrine assays. For sample preparation, plasma was transferred into a conical bottom polypropylene tube containing sodium metabisulfite solution and the internal standard, norephedrine HCl (phenylpropanolamine). All analytes were isolated through liquid-liquid extraction by using an organic solvent. The extracts were further purified by back extraction with dilute acid before analysis using high-performance liquid chromatography-tandem mass spectrometry. A set of calibration standards with varying concentrations of the drugs was also prepared and subjected to the same cleanup procedure. The analytes were separated on a reversed phase column (Atlantis dC18; Waters Corporations, Milford, MA) by using acetonitrile and 0.1% formic acid under gradient condition. Quantitation of the drugs was performed by using multiple reaction monitoring (MRM) in positive ionization mode. Phenylephrine and ephedrine were monitored at m/z 168 → 150 and m/z 166 → 148, respectively (API2000; Applied Biosystems, Foster City, CA). The internal standard, norephedrine HCl, was monitored at m/z 152 → 134. Blank plasma showed no interfering peak at the retention time of the analytes studied. The limits of detection for phenylephrine and ephedrine were 0.2 ng/ml and 0.05 ng/ml, respectively, based on a signal-to-noise ratio of 3. Good linear responses were obtained for both phenylephrine (0.2–50 ng/ml) and ephedrine (0.05–500 ng/ml), with correlation coefficient values 0.9960 and 0.9990, respectively. The within-day variation (intraassay) for phenylephrine ranged from 3.90% to 8.90% (mean 6.39%), whereas that of ephedrine ranged from 2.54% to 7.25% (mean 4.93%). The between-day variation (interassay) for phenylephrine ranged from 7.02% to 10.90% (mean 8.88%), whereas that of ephedrine ranged from 4.41% to 8.03% (mean 6.14%). Samples containing ephedrine at a concentration that was outside the calibration curve were diluted with blank plasma and reassayed.

Subsequent to the completion of the initial analysis, it was discovered that norephedrine, the internal standard, was one of the metabolites of ephedrine. Therefore, to ensure accuracy of the results, a secondary analysis was performed. Leftover plasma samples were retested to determine the amounts of norephedrine metabolite present and to quantify its effect on calculated values for ephedrine. To eliminate the area of norephedrine metabolite from the results, aliquots of leftover samples were retested without the addition of external norephedrine. The area of the metabolite and ephedrine was used to obtain the ratio of metabolite over ephedrine (ratio = area of metabolite/area of ephedrine). This ratio was then used to calculate the area of metabolite present in the original assays (area of metabolite in sample = ratio × area of ephedrine). This enabled the area of external norephedrine added as internal standard to be obtained (actual area of norephedrine = apparent area of norephedrine − area of metabolite). By using the new values of norephedrine area, the ephedrine concentrations of samples were then recalculated. This technique was applied to 121 samples for which leftover plasma was available. The results showed that effect of the presence of the norephedrine metabolite in the samples was small, with adjusted values greater than the original values by a mean difference of 2.07% (SD 1.98%). This correction factor was applied to the originally calculated values for which leftover sample was not available (n = 28). All results are given as adjusted values. The values for MA/UV and UA/UV concentration ratios calculated by using adjusted values were virtually identical to values calculated using the original values.