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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.*<sup>1</sup> 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.<sup>2</sup> 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.*<sup>1</sup> and Dyer *et al.*,<sup>2</sup> as well as the editorial by Smiley,<sup>3</sup> 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:

- 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.
- Phenylephrine can cause bradydysrhythmias that require treatment with atropine. This seems to be more of a problem when an infusion is used.
- 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).<sup>4</sup> Compare those with the values reported in the two studies recently published in *ANESTHESIOLOGY*<sup>1,2</sup> (table 1).
- One study suggests that Apgar scores are a better measure of neonatal outcome than umbilical cord blood gases.<sup>5</sup> 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.<sup>6-13</sup>

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.<sup>10</sup>

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

**Table 1.** Umbilical Artery pH and Base Excess from Two Studies Comparing Ephedrine and Phenylephrine for the Treatment of Hypotension during Cesarean Delivery with Spinal Anesthesia

Phenylephrine	Ephedrine	Parameter Measured	P Value	Reference
7.33 (7.30–7.35)	7.25 (7.14–7.29)	$\mu$ A pH	< 0.001	1
–1.9	–4.8	Base excess		1
7.31	7.28	uA pH	NS	2
–1.34	–4.75	Base excess		2

The values are given as mean (range).

NS = not significant.

such data are available, do not “throw away” the ephedrine syringe, but rather use a common sense approach based on sound clinical judgment when treating maternal hypotension in this setting.

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## In Reply:

I thank Drs. Kempen, Gambling, and McLaughlin for their interest and comments concerning the articles by Ngan Kee *et al.*<sup>1</sup> and Dyer *et al.*<sup>2</sup> regarding phenylephrine infusions during spinal anesthesia for cesarean section and my editorial<sup>3</sup> about the relative lack of acceptance of phenylephrine, especially as an infusion, for the treatment or prevention of hypotension and other side effects in that clinical context.

Dr. Kempen provides a detailed and interesting discussion of the clinical and research protocol followed by the Ngan Kee group and raises possible alternative pharmacokinetic explanations for some of the findings. Many of these points were raised in the review process (of which I was a part), including issues concerning the dosing strategy and the determination of the “baseline blood pressure” in the operating room, as opposed to preoperatively as is perhaps more usual in studies of this kind. On balance, the other reviewers and I believed that the information obtained from the study far outweighed any limitations. Dr. Kempen refers to the dosing strategy in the study by Ngan Kee *et al.* as “high-dose vasopressor therapy for ASA1–2 [American Society of Anesthesiologists physical status 1 and 2] [patients],” suggesting that these healthy women were overtreated or unnecessarily treated to prevent hypotension. I had discussed this type of objection to phenylephrine infusions; basically that this is usually not a “life and death issue” and that the clinical differences compared with older, perhaps simpler, therapies (*e.g.*, bolus ephedrine) are small.<sup>3</sup> The thrust of my opinion was that I disagree with this view; obstetric anesthesiologists have been searching for a solution to the spinal hypotension problem for decades (hence the “Holy Grail” metaphor), and it is notable that when a reasonable solution appears within grasp, fewer clinicians than expected are using it or are even aware of the evidence for its safe use. Dr. Kempen states that there was an increased incidence of hypertension in the phen-

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