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In Reply:

We thank the correspondents for their interest in our article.[1] A number of points were raised, which we shall address in turn.

Dr. Kempen describes our methodology as "questionable" and criticizes us for providing limited disclosure and analysis of hemodynamic data. It would seem that he misunderstands the main objective of our study, which was, as stated, 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. As detailed in the article, our study used a regimen for infusing vasopressors that we have previously described.[2–5] In recent studies by our group[2–5] and others,[3,4] the hemodynamic effects of phenylephrine given by infusion, both in comparison with and in combination with ephedrine, have been well delineated, and a thorough analysis has been provided for hemodynamic parameters, including detailed assessment of accuracy of blood pressure control.[5,6] Because this information is already published, we considered that a detailed repetition of these analyses in our article was not relevant to the objectives of the study and was of limited extra scientific value. Presumably, this belief was shared by the editor and reviewers who did not request extra data or analysis.

Dr. Kempen criticizes us for deviating from the so-called "standard" or "typical" care and methods. For example, he points out that our protocol (similar to our usual clinical practice) did not include the use of intravenous prehydration or routine supplemental oxygen. We make no excuse for this because we consider these practices are supported by little scientific evidence.[7–10] Just because something has been done for a long time does not mean it is right. Dr. Kempen stated that we provided no indication of the number of patients given oxygen, but careful reading of our article reveals this information in the final sentence of the results.

We titrated vasopressors to maintain maternal blood pressure near to baseline values. Our estimations of the latter were indeed derived from "on the table" initial recordings after arrival in the operating room. We acknowledge that this may not be ideal, but we were careful to make multiple measurements, continued this until a degree of stability was achieved, and then averaged three recordings. Dr. Kempen suggests that it may have been better to rely on clinical outpatient measurements, but one might levy equal criticism at what would likely be single measurements using different equipment taken in nonstandardized hospital conditions. In addition, Dr. Kempen states that Chinese exhibit lower pressures than Americans but provides no reference for this. The calculated mean baseline systolic blood pressure for patients in our study was 114 mmHg (SD, 9.9 mmHg). We would not regard this as being particularly low (from being Chinese) or high (from being anxious).

We agree that oscillometric measurement of blood pressure is prone to motion artifact, but we persist in using this method because it remains the most common method in clinical practice. We agree that mean arterial pressure may be a better indicator of perfusion pressure, but nevertheless, systolic pressure remains a clinically useful endpoint on which to base therapy,[11] and many clinicians and researchers continue to use it. Interestingly, Dr. Kempen refers to measurement of blood pressure in "Torr." Our equipment is calibrated in millimeters of mercury, which numerically is close to "Torr" but is not exactly equivalent.*

Dr. Kempen states incorrectly that we "simply stopped" the infusion if systolic blood pressure was greater than base-

* http://www.npl.co.uk/engineering-measurements/mass-force-pressure/pressure/units/pressure-units. Accessed December 18, 2009.

line. In the methodology, we specified that the infusion was in fact titrated using an on/off algorithm according to whether blood pressure was above or below baseline. The exception to this was in the first 2 min when we preferred to maintain a continuous infusion, which was only stopped if the blood pressure was greater than 120% of baseline. In our experience, the greatest hemodynamic instability occurs in the first few minutes after spinal injection. During this period, patients are prone to sudden hypotension, which is often accompanied by distressing nausea, vomiting, and/or dizziness. This can be largely prevented by ensuring an adequate initial dose of phenylephrine, accepting that, given the unpredictability of individual response, in some patients, blood pressure may transiently increase above baseline. Dr. Kempen asks which is worse: hypertension or hypotension? This is difficult to answer, but in our clinical practice, we normally prioritize prevention of hypotension because this is unpleasant for patients, whereas in healthy elective parturients, we have not demonstrated harm from transient spikes of blood pressure above baseline, provided the administration of phenylephrine, a short-acting agent, is discontinued appropriately.[11]

Dr. Kempen suggests that our study represents vasopressor "overuse" and that our report is one of "hypertensive therapy." He makes comparison with "typical clinical care" when classically 100 Torr or a 10–20% drop in systolic from baseline is deemed appropriate. However, this "typical care" has been criticized.[12] From our previous work,[11] we believe that patients are more comfortable when phenylephrine is titrated with the objective of maintaining their blood pressure near baseline rather than targeting lower values such as 90% or 80% of baseline, probably because invariably there will be episodes when blood pressure decreases below the target value. It should be noted that in our study, the context of a randomized double-blinded clinical trial necessitated administration of the vasopressors according to a rigid protocol. In normal clinical practice, one has freedom to control the phenylephrine infusion with more flexibility, tailored to individual responses.

In his editorial,[13] Dr. Smiley mentioned that a variety of specific dosing strategies can be used and have been reported for phenylephrine infusions. We agree that this is important, given the likelihood of differences in anesthetic technique and anthropometric characteristics, and fully support individual modification of our technique.

The total volume of vasopressor given was indeed greater in the phenylephrine group compared with the ephedrine group. The dosing regimens were based on best available data for equipotency. In our article, we commented on the difficulty of comparing potency of drugs that differ in speed of onset and duration of action. Our protocol allowed for rescue boluses of phenylephrine to be given as required if more than two consecutive episodes of hypotension occurred, and the number of patients who required this was shown in table 4 of our article. In our study, only 1 of 52 patients in the phenylephrine group required a single rescue bolus (3 min after spinal injection), whereas 11 of 52 patients in the ephedrine group required rescue boluses (8 patients required 1 bolus, 2 required 2 boluses, and 1 required 3 boluses). Of all the boluses given in the ephedrine group, 14 of 15 patients were given in the first 6 min after spinal injection, with 1 bolus given at 20 min. Dr. Kempen suggests that this introduces potentially confounding issues that detract from our findings because some patients received both vasopressors. On the contrary, we submit that these findings actually enhance our support for the use of phenylephrine because they are further evidence of the inferior efficacy of ephedrine *versus* phenylephrine for maintaining blood pressure. The comparative effects of ephedrine and phenylephrine on fetal acid–base status have been well described previously[14] and do not require repetition. Dr. Kempen questions whether the additional rescue doses of phenylephrine given to patients in the ephedrine group may have contributed to the differences in blood gases. This is unknown, but we believe that, if anything, this would have reduced rather than enhancing the differences by providing better restoration of blood pressure and reducing subsequent ephedrine requirements compared with the alternative therapy of persisting with ephedrine alone.

Dr. Kempen points out that delivery of vasopressors by infusion introduces the risk of inadvertent overinfusion. This is a valid point. Therefore, this technique should only be used by anesthesiologists who are familiar with and skilled in the operation of syringe pumps. Conversely, it should be noted that bolus administration also requires vigilance and may be associated with a greater incidence of hypotension and maternal symptoms.[2] An alternative solution is the use of automated computer-controlled infusion systems that we are currently developing.[5]

We agree that some caution should be exercised when extrapolating our findings to preeclamptics or others (with uteroplacental compromise). We have previously suggested a cautious approach and the use of lower infusion rates in such patients.[15] We and Dr. Smiley[13] concur that more work in this area is needed.

Dr. Kempen is correct that we did not consider the use of traditional Chinese medicine in our patients. Whether this had any effect on hemodynamic responses in our patients remains unknown. Does this substantially affect the validity of extrapolation of our findings to non-Chinese patients? We don't think so. In his editorial, Dr. Smiley did caution against the fact that a large proportion of the research supporting the use of phenylephrine has come from our unit (in which the majority of patients are ethic Chinese).[13] However, he qualified his comments with the referenced observation that our work has been corroborated by work from other countries.

As a clinician, Dr. Kempen alludes to a possible subtle warning from the occurrence of a single Apgar score of less than 7 in the phenylephrine group. We are also clinicians and advise against jumping to conclusions from a single Apgar score of 6 at 1 min. This low Apgar score is most likely explained by the fact that in this particular case, delivery was difficult, and the uterine incision-to-delivery interval (6 min 16 s) was the greatest for all patients in the study.

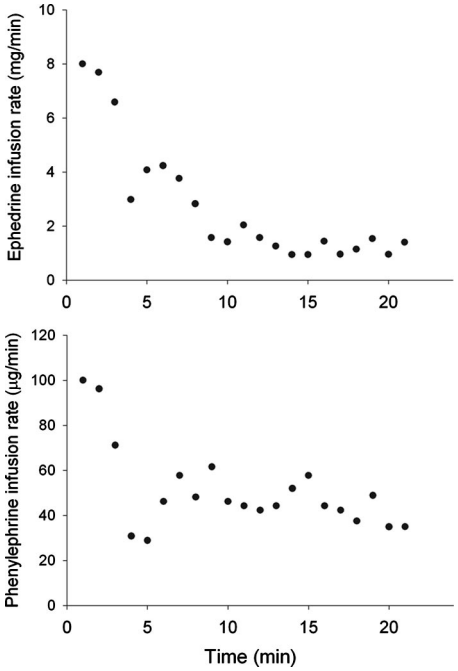

Fig. 1. Mean infusion rate per minute of ephedrine (*top plot*) and phenylephrine (*bottom plot*) from the previous study.[1] Infusion rate decreased with time for both ephedrine ($r = -0.83$, $P < 0.0001$) and phenylephrine ($r = -0.56$, $P = 0.009$).

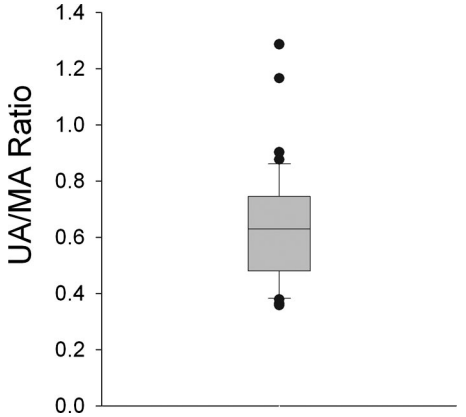

Fig. 2. Umbilical arterial to maternal arterial (UA/MA) ratios of estimated unionized plasma concentrations of ephedrine. Values were calculated by application of the Henderson-Hasselbalch equation to measured data from the previous study.[1] *Box plots* display the 25th, 50th, and 75th percentiles as *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*.

The essential finding of our study was that the umbilical venous/maternal arterial (MA) ratios for phenylephrine were small, indicating that this drug does not readily cross the placenta, whereas the umbilical venous/MA ratios for ephedrine were large, indicating that this drug does readily cross the placenta. This is entirely consistent with consideration of the comparative molecular structures of these drugs. The greater placental transfer of ephedrine and the observed effects on the measured biochemical markers support our theory that well-documented depression of fetal pH and base excess associated with ephedrine is caused by direct metabolic effects of this drug on the fetus. An additional interesting observation was that the mean umbilical venous/MA ratio for ephedrine was greater than unity. In our article, we suggested that a possible explanation for this may have been ion trapping. However, we concede that this explanation was speculative and welcome further explanations as suggested by Drs. Kempen and Cooper.

Dr. Cooper provides evidence from his own work on vasopressor infusions showing that drug requirements decreased during the time until delivery and that this occurred to a greater extent with ephedrine compared with phenylephrine. We reanalyzed our data and found a similar result. In figure 1, we have plotted mean vasopressor consumption per minute *versus* time. It can be seen that consumption decreased with time with both drugs, but the trend was greater for ephedrine ($r = -0.83$, $P < 0.0001$) compared with phenylephrine ($r = -0.56$, $P = 0.009$). However, although this may suggest the possibility of reverse maternal/fetal concentration gradients for ephedrine, we believe that the associated diffusion kinetics are unlikely to be simple, as implied by Dr. Kempen.

First, to accept that reverse fetal–maternal diffusion occurs would imply that ephedrine readily crosses the placenta; this would further support our primary findings. Second, it is important to consider redistribution within the fetus. It is simplistic to consider the fetus as a single compartment (although the senior author during his diaper-changing period of life was convinced that this becomes the case soon after birth!). Ephedrine transferred to umbilical venous blood would be expected to undergo distribution and metabolism in the fetus. Conditions conducive for ephedrine to diffuse from the fetal circulation back to the maternal circulation would require a gradient where umbilical arterial (UA) concentrations are high relative to MA concentrations. Reanalysis of our data shows some support for this because the UA/MA ratio for ephedrine concentration was greater than 1 in 15 of 45 patients for whom data were available. However, one must also consider that ephedrine is a weak base (pKa, 9.6) that exists in both unionized and ionized forms, the relative proportions of which will differ between the mother and fetus because of pH differences. If one assumes that placental transfer occurs by simple passive diffusion, then the gradient of importance is that between concentrations of unionized drug species in UA and MA blood. The latter can be calculated by applying the Henderson-Hasselbalch equation:

$$\log \frac{[\text{unionized}]}{[\text{ionized}]} = \text{pH} - \text{pKa}$$

Applying this to our data, we found that unionized ephedrine concentrations were greater in UA *versus* MA blood in only 2 of 41 patients for whom data were available (fig. 2). This may be simplistic, given that drug diffusion is dynamic rather than static, and our methodology provided only single point measurements of drug concentrations at the time of delivery. However, accepting these limitations, our

data show little evidence of conditions favorable to fetal-to-maternal diffusion of ephedrine.

Dr. Gambling is as ever, with his associate, a voice of reason. We agree that the use of ephedrine in obstetrics should not be completely discontinued. However, we strongly believe that phenylephrine has earned a place as a first-line agent, which is supported by the results of clinical trials published by ourselves and others.

Drs. Gambling and Mclaughin state that phenylephrine is not always effective, but in our experience, this is seldom the case. It may be a matter of using an adequate dose because there is evidence that initial dose requirements of phenylephrine may sometimes be substantially greater than typically used.[16,17] Indeed, phenylephrine causes baroreceptor-mediated slowing of heart rate. This may also decrease cardiac output.[18] However, the clinical importance of this is uncertain, and in our practice, we normally tolerate heart rates as low as 50 beats/min. We suggest caution with the use of anticholinergics because concurrent administration with phenylephrine may result in hypertension. One exception is the occasional patient who suffers simultaneous hypotension and bradycardia. In this situation, the use of ephedrine may be more appropriate than phenylephrine, given together with intravenous fluid to maintain cardiac filling.

We agree that in healthy elective cases, it is difficult to determine the clinical significance of the observed depression of fetal pH and base excess associated with large doses of ephedrine, but the fact that these biochemical outcome measures are better with phenylephrine has given us confidence to use phenylephrine in doses necessary to prevent maternal symptoms such as nausea and vomiting and, we believe, improve the maternal experience. Some pH and base excess values can be alarmingly low when large doses of ephedrine are used. Drs. Gambling and Mclaughin present data from our study and invite comparison with data from uncomplicated vaginal deliveries. However, they have misread the table in our original publication in which values for interquartile range, not range, were presented. The ranges for UA pH and base excess were in fact 6.913–7.329 and −17.3 to −0.5, respectively, for patients who received ephedrine. Of note, there were five cases with both UA pH of less than 7.1 and base excess of less than −12 mmol/l; these values are well below the range that what we would normally expect from normal deliveries. Although Drs. Gambling and Mclaughin cited work suggesting that Apgar scores are a better measure of neonatal outcome than umbilical cord gases,[19] it is important to place that work in context. The main finding of the cited study was that 5-min Apgar scores of 0–3 were associated with greater risk of neonatal death compared with scores of 7–10. The relevance of these findings to elective cesarean delivery is uncertain. Although it is true that studies comparing vasopressors have not shown significant differences in Apgar scores or other measures of clinical outcome, this does not necessarily mean that umbilical cord blood gases results are without worth. Dr. Smiley described the vasopressor choice issue as "not being quite a life and death issue."[13] We believe that few modern advances in obstetric anesthesia care are likely to fit this category.

Drs. Gambling and Mclaughin suggest the use of ephedrine and phenylephrine in combination. However, when administered by infusion, we were unable to demonstrate any advantage of this technique compared with the use of phenylephrine alone.[6] They also suggest that it may be prudent to use phenylephrine in nonelective cesarean deliveries. Our previous study of such patients[20] had mixed results, and this remains an area of uncertainty. Laboring patients are more hemodynamically stable during spinal anesthesia compared with nonlaboring patients, and thus it is unusual for large doses of vasopressors to be required.

During more than 10 yr of research in this topic, we have found infusions of phenylephrine to be the most useful method for maintaining maternal blood pressure during spinal anesthesia for cesarean delivery, with no discernable adverse effects on the fetus. For us, this technique has passed the research acid test in that we have successfully applied the results of our research to our everyday clinical practice and find that hypotension is no longer an important clinical problem. Perhaps not the Holy Grail, but also no humbug.

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In Reply:

We thank Dr. Gambling *et al.* for their interesting and pertinent comments. Parturients presenting for spinal anesthesia for elective cesarean delivery are not only fluid replete but also have the expanded blood volume of pregnancy. In a recent investigation, we demonstrated that the initial 20% decrease in mean arterial pressure after induction of spinal anesthesia was associated with a partial compensatory increase in maternal cardiac output mediated by an increase in stroke volume and heart rate, provided adequate lateral tilt was used and a rapid crystalloid coload was administered.[1] In this scenario, phenylephrine seems to be the ideal initial vasopressor, in that the correction of systemic vascular resistance reduces cardiac output and increases blood pressure to levels approaching baseline values. In addition, blood pressure is restored more rapidly after phenylephrine than ephedrine, and this could prevent maternal symptoms, in particular nausea and vomiting. Heart rate was found to be a good surrogate marker of maternal cardiac output. Doses of phenylephrine causing a marked increase in blood pressure and sinus bradycardia significantly depress maternal cardiac output below baseline values and should be avoided.

We agree that, in certain circumstances, the rapid onset β-adrenergic effects of ephedrine have an important role to play. In particular, in the small proportion of patients in whom the response to spinal anesthesia is bradycardia and hypotension (which indicates a decreased cardiac output), anticholinergics or ephedrine would seem to be a much better choice, once the uterus has been adequately displaced. In low-resource environments in which preoperative maternal assessment is sometimes less than ideal, the beta effects of ephedrine may be important in undiagnosed cases of ventricular dysfunction in which the hemodynamic response to spinal hypotension is inadequate.[2]

We agree that in most cases of spinal hypotension in which the fetus is healthy, the minor degree of fetal acidosis induced by ephedrine is probably clinically insignificant. Indeed, a minor degree of stimulation of metabolic activity may be beneficial.[3] However, it is probable that if the fetus is compromised and there are further complications such as maternal hypotension and a long uterine incision to delivery time, large doses of ephedrine are to be avoided because an increase in fetal metabolic rate could adversely affect the oxygen supply to demand ratio. It should also be noted that the median doses of vasopressor used predelivery in the recent article to which Dr. Gambling alludes, namely 61 mg of ephedrine and 1,300 μg of phenylephrine, are considerably higher than those used by most clinicians in clinical practice.[4]

Therefore, in summary, we agree with Dr. Gambling that phenylephrine given in doses adequate to restore the baseline heart rate is the vasopressor of choice in most cases and that ephedrine has an important role to play when indicated by the maternal hemodynamic response to spinal anesthesia.

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