

majority of rats in our experiment recovered well from the neurosurgery, with normal appetite and defecation.

Third, we admit that we neglect the potential problem of using chloral hydrate for euthanasia of rats. Chloral hydrate is a traditional anesthetic in animal experiments, and before we performed our study we also found that it is used for killing rats by either decapitation or cardiac perfusion in respectable published articles.^{2,5,6} Moreover, our research was approved by the Institutional Animal Care and Use Committee with no questions. Therefore, we never doubted the use of chloral hydrate for rat euthanasia. Now we feel deeply sorry for the possibility of inflicting pain on the animals because of using chloral hydrate.

Finally, we would like to extend our sincere gratitude to Baxter *et al.* for letting us understand animal euthanasia more deeply. We will pay much more attention to the euthanasia issue, adopt proper and scientific animal welfare methods, and try our best to decrease harm to the experimental animals as much as possible in future research.

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Low-dose Spinal Anesthesia with Low-dose Phenylephrine Infusions for Cesarean Delivery: Better but Not Necessarily Best

To the Editor:—We read with interest the recently published report by Langesæter *et al.*¹ together with the accompanying editorial,² describing the use of minimally invasive continuous cardiac output monitoring during spinal anesthesia for cesarean delivery. Based on derived values for cardiac output, the authors advocated allowing a 10 to 20% decrease in blood pressure and questioned as unnecessary the use of higher doses of phenylephrine given to maintain blood pressure near baseline. The findings from this paper are important and are a substantial contribution to our knowledge of the hemodynamic changes during regional anesthesia in parturients. However, we believe that some caution is required when extrapolating these findings to recommendations for everyday clinical practice.

Although placement of peripheral arterial catheters was regarded as “minimally invasive,” we believe that most clinicians would find them difficult to justify in routine elective cases and will continue to rely on the use of noninvasive blood pressure monitoring, despite its intermittent nature of measurement. From our previous work, we consider that, when using noninvasive blood pressure monitoring, the clinically optimal approach is to titrate a phenylephrine infusion with the target of maintaining systolic blood pressure near to the baseline value. Using this approach, with both manual³⁻⁵ and automated⁶ control, the incidence of nausea and vomiting is significantly reduced, as compared with less strict blood pressure control⁴; this is a clearly defined and important endpoint, the clinical relevance of which is more immediately apparent as compared with derived values for cardiac output.

When using phenylephrine to maintain maternal blood pressure, it is important to appreciate that although this potent vasopressor has a faster onset and can be more accurately titrated than ephedrine,⁷ control is not perfect and some variation (overshoot and undershoot) between target and actual blood pressure is to be anticipated. For example, in a previous study,⁴ when we targeted a systolic blood pressure of 80% of baseline (equivalent to allowing a 20% decrease as advocated by Langesæter *et al.*¹), in actuality in the first 15 min after intrathecal injection, 96% of patients had one or more measurements < 80% of baseline with 25% of all measurements < 80% (fig. 1), and 52% of patients had one or more measurements < 70% of baseline with

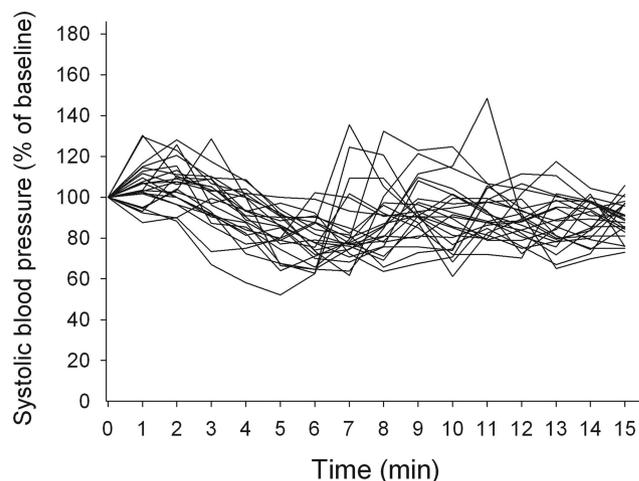


Fig. 1. Changes in systolic blood pressure in the first 15 min after spinal anesthesia in patients having cesarean delivery with a phenylephrine infusion titrated with the target of maintaining values at the target of 80% of baseline. Twenty-five percent of all measurements were < 80% of baseline and 7% of all measurements were < 70% of baseline.⁴

7% of all measurements < 70%. As a consequence, 40% of patients experienced nausea or vomiting. In comparison, when we targeted a systolic blood pressure of 100% of baseline, 29% of patients had one or more measurements < 80% of baseline with 4.7% of all measurements < 80%; 8% of patients had one or more measurements < 70% of baseline with 2% of all measurements < 70%; and only 4% of patients experienced nausea or vomiting. Phrased in another way, our results suggest that to maintain maternal comfort, phenylephrine should be titrated whenever blood pressure begins to decrease. Delaying or withholding administration while permitting a decrease in blood pressure to some arbitrary percentage threshold below baseline as suggested by Langesæter *et al.*¹ risks the likelihood that blood pressure

will decrease further below the threshold and result in unpleasant symptoms.

Data from Langesæter *et al.*¹ suggest that liberal administration of phenylephrine to achieve tight blood pressure control may result in lower cardiac output than a less aggressive approach. However, the clinical relevance of this in healthy elective patients is undetermined. Dyer and James² stated that heart rate and blood pressure are used clinically as surrogate markers of maternal cardiac output, and that maximum changes in the latter correlate better with uteroplacental blood flow than with upper arm blood pressure. However, it has yet to be proven whether a global measure of cardiac output is the ideal parameter on which to base hemodynamic therapy in obstetric patients, since this does not necessarily represent regional flow in the uterus and placenta, which have widely dilated vasculature through which flow is largely pressure-dependent.⁸ Furthermore, studies in animals that have correlated fetal oxygen uptake with uterine blood flow have demonstrated that, under normal physiologic conditions, uterine blood flow is in excess of the minimum required to satisfy fetal oxygen demand.⁹ This confers a margin of safety that, to a degree, protects the fetus from fluctuations in uterine blood flow.¹⁰ If the same situation occurs in humans it could explain the lack of fetal acidosis observed when large doses of phenylephrine are used to maintain maternal blood pressure,³⁻⁵ despite evidence that this drug has the potential to decrease both cardiac output and uteroplacental blood flow. The implication of this is that in healthy parturients, within limits, even if hemodynamic control using phenylephrine does slightly reduce cardiac output and uteroplacental blood flow, it may still be clinically acceptable if this is balanced against other benefits such as maternal wellbeing.

Langesæter *et al.*¹ concluded that that low-dose bupivacaine (with sufentanil), combined with a low-dose infusion of phenylephrine and moderate cohydration, gives the "best" hemodynamic stability. However, they can only validly make comparisons among the actual regimens included in their study. Because there were no direct comparisons with patients who received higher doses of phenylephrine or larger volumes of cohydration, it is speculative to assume that any of their regimens were superior to these other possible regimens. Moreover, a large proportion of their patients who received a low-dose phenylephrine infusion required supplementary boluses of vasopressors. Thus the mean phenylephrine requirement per patient was somewhat greater than the baseline $0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and it cannot be excluded that a higher infusion rate may have provided more stable hemodynamic control. Also, when assessing the optimal regimen for hemodynamic control, we believe that ease of use is also a factor to be considered. In that respect, we consider a vasopressor infusion that is titrated to a defined endpoint to be superior to the use of a hybrid technique of a fixed rate low-dose infusion to which is added

repeated "rescue" boluses for times when the infusion is inadequate. This is especially relevant during single-shot spinal anesthesia when small intrathecal doses as used by Langesæter *et al.*¹ may not be appropriate.

We continue to advocate aggressive maintenance of blood pressure using phenylephrine in women having elective cesarean delivery under spinal anesthesia. Although it may be possible that cardiac output is slightly less with this method as compared with allowing blood pressure to drift 10 to 20% below baseline, unless evidence is produced that this is associated with a clinically important decrease in uteroplacental blood flow *and* with a detrimental effect on neonatal outcome, we believe that improved maternal comfort justifies our technique.

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Maternal Hemodynamic Monitoring and the Vigileo Monitor

To the Editor:—We read the recent editorial by Dyer and James,¹ referencing the paper by Langesæter *et al.*² with great interest. Langesæter *et al.*² have successfully demonstrated that a minimally invasive technology that measures cardiac output (LiDCOplus, LiDCO Ltd., Cambridge, United Kingdom) can be used for maternal hemodynamic monitoring. Other arterial pressure waveform-based systems that provide beat-by-beat assessment of cardiac output and stroke volume include the PiCCOplus (Pulsion Medical Systems, Munich, Germany) and the Vigileo monitor/FloTrac sensor (Edwards Lifesciences LLC, Irvine, CA). Dyer and James¹ note in their editorial that these less invasive methods of hemodynamic monitoring are attractive to the obstetric anesthesiologist. However, the editorial¹ view that the

Vigileo monitor is unsuitable for the study of rapid maternal hemodynamic changes is not a logical conclusion.

Bland-Altman analysis is routinely used to assess precision and bias when comparing two different measurement techniques.³⁻⁹ As acknowledged in the editorial, the acceptance of a new technique of cardiac output measurement should rely on limits of agreement of up to $\pm 30\%$ between the minimally invasive techniques and the existing "gold-standard" (*i.e.*, the thermodilution pulmonary artery catheter).⁵ There are currently several studies in the critical care and cardiac anesthesia literature that have evaluated precision and bias (using Bland-Altman analyses) in the measurements of cardiac output with the Vigileo monitor/FloTrac sensor.^{3,4,7-10} Based on these studies, statisti-