

Phenylephrine Added to Prophylactic Ephedrine Infusion during Spinal Anesthesia for Elective Cesarean Section

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Background: Because ephedrine infusion (2 mg/min) does not adequately prevent spinal hypotension during cesarean delivery, the authors investigated whether adding phenylephrine would improve its efficacy.

Methods: Thirty-nine parturients with American Society of Anesthesiologists physical status I-II who were scheduled for cesarean delivery received a crystalloid preload of 15 ml/kg. Spinal anesthesia was performed using 11 mg hyperbaric bupivacaine, 2.5 µg sufentanil, and 0.1 mg morphine. Maternal heart rate and systolic blood pressure were measured at frequent intervals. A vasopressor infusion was started immediately after spinal injection of either 2 mg/min ephedrine plus 10 µg/min phenylephrine or 2 mg/min ephedrine alone. Treatments were assigned randomly in a double-blind fashion. The infusion rate was adjusted according to systolic blood pressure using a predefined algorithm. Hypotension, defined as systolic blood pressure less than 100 mmHg and less than 80% of baseline, was treated with 6 mg ephedrine bolus doses.

Results: Hypotension occurred less frequently in the ephedrine-phenylephrine group than in the ephedrine-alone group: 37% versus 75% ($P = 0.02$). Ephedrine (36 ± 16 mg, mean \pm SD) plus 178 ± 81 µg phenylephrine was infused in former group, whereas 54 ± 18 mg ephedrine was infused in the latter. Median supplemental ephedrine requirements and nausea scores (0-3) were less in the ephedrine-phenylephrine group (0 vs. 12 mg, $P = 0.02$; and 0 vs. 1.5, $P = 0.01$, respectively). Umbilical artery pH values were significantly higher in the ephedrine-phenylephrine group than in the group that received ephedrine alone (7.24 vs. 7.19). Apgar scores were similarly good in both groups.

Conclusion: Phenylephrine added to an infusion of ephedrine halved the incidence of hypotension and increased umbilical cord pH.

PROPHYLACTIC intravenous ephedrine, given either in small bolus doses or by infusion, has been recommended to prevent hypotension after spinal anesthesia during scheduled cesarean delivery.¹⁻⁸ However, recent studies

have challenged the efficacy of this approach.⁹⁻¹⁴ In addition, in many studies prophylactic ephedrine was associated with lower umbilical cord pH,^{7,10,12,15-17} particularly when large doses (50 mg administered intramuscularly or 3-4 mg/min administered intravenously) were used.^{12,15}

Despite earlier concerns that phenylephrine might cause uteroplacental vasoconstriction,¹⁸ it was shown to be safe using low doses in pregnant animals.¹⁹ More recently, clinical trials have confirmed the effectiveness of phenylephrine for treatment of hypotension in parturients undergoing scheduled cesarean delivery with epidural²⁰ or spinal anesthesia^{5,21-24} and have found no deleterious effects in these healthy pregnancies. However, phenylephrine used alone may be accompanied by maternal bradycardia^{5,24} and does not benefit from widespread clinical experience, as does ephedrine. Thus, phenylephrine has not yet become popular, particularly for prophylactic use.⁵ Clinical experience suggests that phenylephrine may be useful in addition to ephedrine when the latter fails to correct hypotension.^{4,25} The physiologic rationale for adding phenylephrine to ephedrine is to increase the α/β -agonist activity ratio. This should help to better counteract spinal anesthesia-induced vasoplegia, which impedes venous return and decreases cardiac output.

We thus designed a randomized double-blind study to compare the effectiveness of infusions of ephedrine plus phenylephrine versus ephedrine alone for preventing spinal hypotension during scheduled cesarean delivery. In addition, we measured umbilical cord blood pH and Apgar scores to evaluate neonatal outcome after these two vasopressor regimens.

Materials and Methods

After obtaining approval from review boards at both centers and written informed consent from patients, we enrolled 42 parturients scheduled for cesarean delivery using spinal anesthesia. Inclusion criteria included age 18 yr or older, weight 90 kg or less, height 152 cm or greater, American Society of Anesthesiologists physical status I or II, and term singleton pregnancy. Parturients with pregnancy-induced hypertension, cardiac disease, diabetes, or fetal complications, and those in labor were

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excluded. Patients fasted overnight and were given 30 ml 0.3 M sodium citrate (plus 200 mg effervescent cimetidine in the French center) orally on arrival to the operating room. Oxygen was administered to all patients *via* nasal catheters. Standard monitors included an electrocardiogram, noninvasive blood pressure device, and pulse oximetry.

After an intravenous preload of 15 ml/kg lactated Ringer's solution, spinal anesthesia was performed at the L2-L3 or the L3-L4 interspace with the patient sitting, using a 9-cm 25-gauge Whitacre spinal needle. After clear, free flow of cerebrospinal fluid was obtained, 11 mg hyperbaric 0.5% bupivacaine, 2.5 μ g sufentanil, and 0.1 mg morphine was injected through the spinal needle. Patients were then immediately placed in the recumbent position with left uterine displacement.

A prophylactic vasopressor intravenous infusion was started at the end of spinal injection. Patients received either ephedrine plus phenylephrine (E+P group) or ephedrine alone (E group) at an initial rate of 2 mg/min \pm 10 μ g/min *via* an automated syringe (containing 60 mg ephedrine \pm 300 μ g phenylephrine in a total volume of 20 ml saline started at 40 ml/h). The phenylephrine dosage was chosen taking into account the comparative studies on phenylephrine *versus* ephedrine^{5,20-24} and the series by Taylor and Tunstall.²⁵ These studies suggested a potency ratio of 40-100 μ g phenylephrine to 6 mg ephedrine,^{5,20-24} whereas a dose ratio of only 30 μ g phenylephrine to 6 mg ephedrine should be effective when combining the two drugs.²⁵

The syringe was connected to the infusing intravenous line (Ringer's lactate solution, 250 ml/h) close to the intravenous catheter to avoid equipment dead space. Both the patient and the investigator were blinded to group assignment. Study solutions were prepared by an anesthesiologist or a nurse anesthetist not involved in the patients' care, according to the group indicated in numbered, sealed, opaque envelopes. These envelopes were prepared using a random table with stratification to allocate the same number of patients to the two groups within each center. One of the investigators (S. E. C.) was present during the study period in both centers to confirm comparability of routine procedures.

The primary outcome variable was the incidence of hypotension, defined as systolic blood pressure (SBP) less than 100 mmHg and less than 80% of baseline before delivery. Baseline SBP and maternal heart rate were determined by the average of triplicate measurements obtained before preloading with lactated Ringer's solution. After spinal injection, SBP and maternal heart rate were measured every minute for 10 min and every 2 min thereafter until delivery. A predefined algorithm was used to adjust the syringe rate according to SBP as follows:

- The rate was maintained if SBP remained within 90 and 105% of baseline.
- The rate was halved if SBP increased to between 105 and 120% of baseline.
- The infusion was stopped if SBP increased to more than 120% of baseline (and restarted at 40 ml/h or 80 ml/h if SBP decreased back to between 90 and 105% of baseline or to < 90% of baseline, respectively).
- The rate was doubled (up to 80 ml/h) if SBP decreased to between 80 and 90% of baseline.
- Hypotension (SBP < 100 mmHg and < 80% of baseline) was treated with 6 mg ephedrine bolus doses, repeated as needed.

For each subject, the minimum and maximum SBP and heart rate values observed before delivery were recorded. A back-up plan designed to treat several critical situations (*e.g.*, severe hypotension not responding to ephedrine bolus doses, recurrent hypotension despite cumulative ephedrine bolus doses in excess of 60 mg, and extreme tachycardia or bradycardia not tolerated clinically) allowed the anesthesiologist to administer epinephrine, additional phenylephrine, or atropine as needed.

The upper level of sensory changes 20 min after spinal injection was determined using an alcohol swab. Nausea or vomiting occurring after spinal anesthesia and before delivery was rated using a four-point scale (where 0 = none, 1 = mild nausea, 2 = nausea requiring treatment, and 3 = vomiting). Nausea or vomiting with a score of 2 or 3 was treated with 10-20 mg intravenous metoclopramide if unrelated to hypotension or not corrected by ephedrine bolus doses alone.

Additional data collection included the time intervals from spinal anesthesia to incision, from spinal anesthesia to delivery, and from uterine incision to delivery, the dose of vasopressor (ephedrine with or without phenylephrine) infused until delivery, venous and arterial umbilical cord pH values (obtained from a doubly clamped segment of umbilical cord), neonatal Apgar scores, and neonatal weight.

Data are expressed as mean \pm SD unless stated otherwise. Groups were compared for single parametric, ordinal, and nominal variables using an unpaired Student *t* test, the Mann-Whitney U test, and the Fisher exact test, respectively. Only hemodynamic values obtained before delivery were included in analysis. Hemodynamic values over time were compared using analysis of variance for repeated measures, followed by Dunnett tests to assess differences at each time *versus* time zero within each group. A forward, stepwise regression analysis was performed to determine the association between venous or arterial umbilical blood pH with the following five variables: duration of hypotension, total ephedrine dose, time interval from spinal anesthesia to skin incision, time from spinal anesthesia to delivery, and time from uterine

Table 1. Demographic, Anesthetic, and Obstetric Data

	Group		<i>P</i>
	Ephedrine + Phenylephrine	Ephedrine	
Age (yr)	34 ± 5	33 ± 5	0.7
Weight (kg)	73 ± 10	76 ± 8	0.2
Height (cm)	163 ± 7	165 ± 5	0.4
Gestational age (weeks)	39 ± 0.9	39 ± 0.7	0.2
Weight of neonate (g)	3,273 ± 467	3,437 ± 448	0.3
Upper sensory level*	T2 (T6–C4)	T2 (T4–C4)	0.7
SA to incision (min)	16 ± 5	16 ± 6	0.9
SA to delivery (min)	28 ± 6	29 ± 8	0.7
UI to delivery (s)	113 ± 72	120 ± 50	0.7

Data are mean ± SD, except *: median (range).

SA = spinal anesthesia; UI = uterine incision.

incision to delivery. $P < 0.05$ was considered significant. Sample size calculations indicated that including 37 patients in the study would result in an 80% power to detect a decrease from 75 to 37.5% in the incidence of hypotension at a significance level of 0.05.

Results

Three patients were excluded because of protocol violations (two in the E+P group and one the E group), so that data from 39 patients were available for analysis. One patient in the E group became severely hypotensive (systolic–mean–diastolic pressures: 54–43–31 mmHg; heart rate: 80 beats/min) and almost fainted 7 min after spinal injection. Two 15-mg bolus doses of intravenous ephedrine were given 30 s apart and restored adequate hemodynamic values within 2 min. However, recurrent episodes of moderate hypotension occurred (SBP between 80 and 90 mmHg) despite additional ephedrine bolus doses up to a total dose of 60 mg within 26 min of

spinal injection. According to the back-up plan previously described, the anesthesiologist administered 100 µg phenylephrine, which resolved hemodynamic instability. The neonate in this case had one of the two lowest umbilical cord pH values of the series (7.01) but had normal Apgar scores (9 and 10 at 1 and 5 min, respectively). Another patient (in the E+P group) had a pronounced, but well tolerated, bradycardia (35 beats/min) that resolved in less than 1 min after a single intravenous injection of 0.5 mg atropine plus 12 mg ephedrine. Newborn umbilical venous and arterial pH and Apgar scores were normal in this case (7.46, 7.36, and 10 and 10, respectively).

Patient characteristics, gestational age, neonatal weight, upper sensory level of anesthesia at 20 min, and time intervals from spinal anesthesia to incision, from spinal anesthesia to delivery, and from uterine incision to delivery were comparable between the two groups (table 1). Baseline SBP and maternal heart rate (table 2) were also comparable between the groups.

The incidence of hypotension was halved in the E+P group when compared with the E group (37% vs. 75%, $P = 0.02$; table 2). Minimum SBP values before delivery were lower in the E group, but the difference failed to reach statistical significance ($P = 0.08$). Hypotensive episodes were brief and of similar cumulative duration in both groups (table 2). In addition, SBP values after onset of spinal anesthesia were not significantly different between the two groups (fig. 1); similar results were obtained for mean and diastolic blood pressure (data not shown). Maximum SBP and minimum heart rate before delivery also were comparable in both groups. In contrast, maximum heart rate before delivery was 15 beats/min higher in the E group than in the E+P group ($P = 0.02$; table 2). Furthermore, maternal heart rate after onset of spinal anesthesia was significantly increased in the E

Table 2. Hemodynamic Data

	Group		<i>P</i>
	Ephedrine + Phenylephrine	Ephedrine	
Baseline SBP (mmHg)	119 ± 11	121 ± 9	0.6
Baseline heart rate (beats/min)	82 ± 9	84 ± 11	0.6
Incidence of hypotension (%)	37	75*	0.02
Minimum SBP (mmHg)	99 ± 16	90 ± 13	0.08
Duration of hypotension† (min)	2.0 ± 0.6	2.6 ± 0.5	0.5
Maximum SBP (mmHg)	138 ± 14	143 ± 14	0.3
SBP > 120% of baseline (%)	16	25	0.7
Minimum heart rate (beats/min)	65 ± 11	69 ± 10	0.2
Maximum heart rate (beats/min)	106 ± 14	121 ± 21*	0.02
Phenylephrine infused (µg)	178 ± 81	—	—
Ephedrine infused (mg)	36 ± 16	54 ± 18*	0.002
Supplemental ephedrine‡ (mg)	0 (0–30)	12 (0–60)*	0.02
Total ephedrine (mg)	41 ± 21	68 ± 23*	< 0.001
Nausea‡ (0–3)	0 (0–2)	1.5 (0–3)*	0.01

Data are mean ± SD, except ‡: median (range).

* Significantly different from ephedrine + phenylephrine group. † Cumulative time from spinal injection to delivery for hypotensive patients.

SBP = systolic blood pressure.

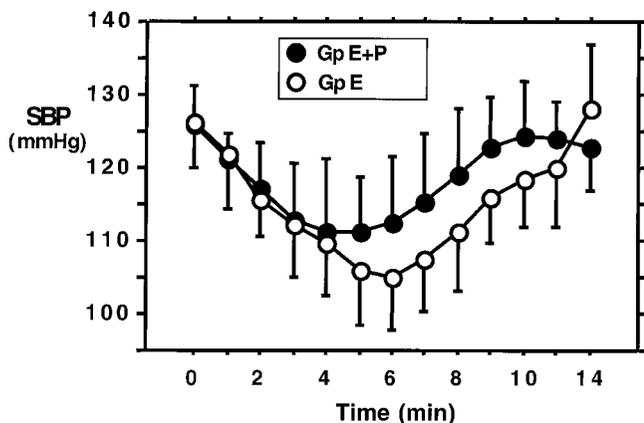


Fig. 1. Maternal systolic blood pressure (SBP) after onset of spinal anesthesia. Vasopressor infusions (ephedrine [E] \pm phenylephrine [P]) were started at the end of spinal injection (time zero). Mean SBP values were not significantly different between the two groups ($P = 0.3$). Data are mean values with 95% confidence intervals.

group from 3 to 6 min after spinal anesthesia ($P < 0.05$ vs. time zero), whereas it remained unchanged in the E+P group (fig. 2). Significantly more ephedrine was infused and more supplemental ephedrine was given in the E group (table 2). Nausea scores were lower in the E+P group (table 2), with 59% of patients in this group completely free of symptoms versus only 30% of patients in the E group.

Umbilical venous and arterial pH values were significantly higher in the E+P group (table 3). The incidence of arterial pH less than 7.20 was 31% in the E+P group and 63% in the E group ($P = 0.09$). However, Apgar scores at 1 and 5 min were similar in both groups and were never less than 7. Venous and arterial umbilical pH

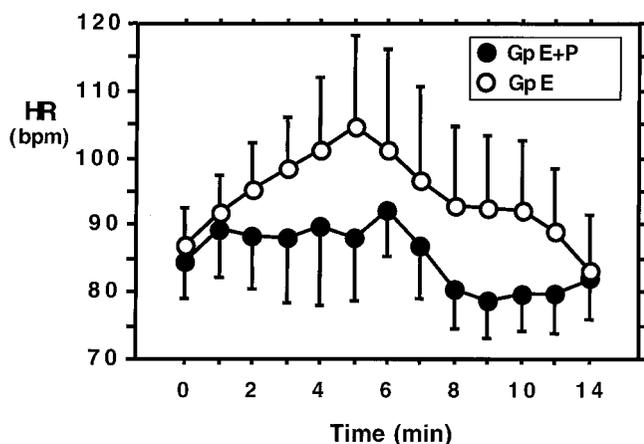


Fig. 2. Maternal heart rate (HR) after onset of spinal anesthesia. Vasopressor infusions (ephedrine [E] \pm phenylephrine [P]) were started at the end of spinal injection (time zero). Maternal HR was significantly lower in the group that received ephedrine plus phenylephrine ($P = 0.03$); maternal HR remained unchanged in this group, whereas it increased in the group that received ephedrine only from 3 to 6 min after spinal anesthesia ($P < 0.05$ vs. time zero). Data are mean values with 95% confidence intervals. bpm = beats/min.

Table 3. Neonatal Outcome

	Group		<i>P</i>
	Ephedrine + Phenylephrine	Ephedrine	
Umbilical venous pH*	7.33 (7.18–7.46)	7.28† (7.11–7.38)	0.03
Umbilical arterial pH‡	7.24 (7.12–7.36)	7.19† (7.01–7.37)	0.05
Apgar score at 1 min	9 (7–10)	9 (8–10)	0.7
Apgar score at 5 min	10 (9–10)	10 (9–10)	0.7

Values are median (range).

* One missing value for umbilical venous pH (in ephedrine group). † Significantly different from ephedrine + phenylephrine group. ‡ Four missing values for umbilical arterial pH (one in ephedrine group and three in ephedrine + phenylephrine group).

values were negatively correlated with the time interval from spinal anesthesia to delivery (adjusted $r = 0.58$ and 0.57 , respectively, $P < 0.001$ in both cases; figs. 3A and 3B). Venous pH was also negatively correlated with the duration of hypotension (adjusted $r = 0.47$, $P = 0.002$), and arterial pH was negatively correlated with total ephedrine dose (adjusted $r = 0.50$, $P = 0.001$). Neither the time interval from spinal anesthesia to skin incision nor from uterine incision to delivery was correlated with venous or arterial pH. Low venous (< 7.20) and arterial (< 7.10) pH values were associated only with E-group assignment and spinal anesthesia to delivery times longer than 33 min (figs. 3A and 3B).

Discussion

Spinal anesthesia has become the preferred technique for scheduled cesarean delivery because of the availability of fine-gauge pencil-point needles and the excellent anesthesia obtained with the addition of spinal opioids to hyperbaric bupivacaine.²⁶ However, hypotension remains a major drawback with this technique, despite maternal positioning to avoid aortocaval compression and various other preventive measures, including crystalloid and colloid infusions.²⁷ Since 1982, prophylactic intravenous ephedrine administered either by infusion^{2,4,6,8} or bolus doses^{1,7} has been considered the gold standard for preventing hypotension. However, other studies have challenged the efficacy of this technique. Olsen *et al.*⁹ concluded that although mean arterial blood pressure tended to decrease less in parturients who had received prophylactic intravenous ephedrine (0.15-mg/kg bolus dose plus $0.4\text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), this did not adequately prevent hypotension. King and Rosen¹¹ reported that neither ephedrine bolus doses alone nor an ephedrine bolus dose plus an infusion (10 mg bolus $\pm 10\text{ mg}$ infused over 10 min) decreased the incidence of hypotension, which remained at 60%. Tsen *et al.*¹⁴ similarly found that a 10-mg bolus of ephedrine did not prevent hypotension (70% incidence). Ngan Kee *et al.*¹³

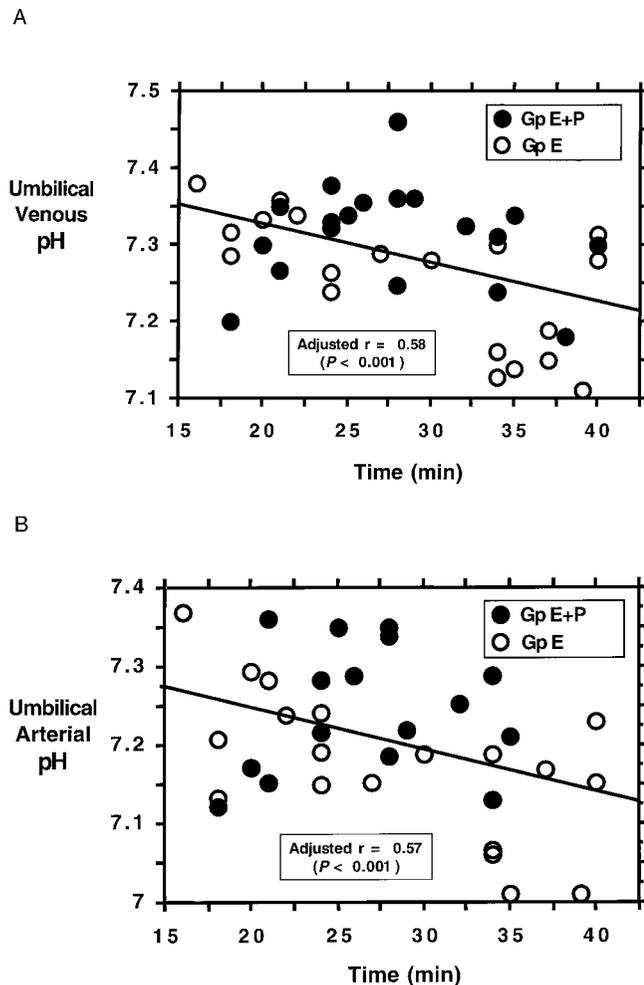


Fig. 3. (A) Correlation between time from spinal anesthesia to delivery and umbilical venous pH. The two variables were negatively correlated with adjusted $r = 0.58$ ($P < 0.001$). Low venous pH values (< 7.20) were associated only with assignment to the ephedrine-only group and time from spinal anesthesia to delivery longer than 33 min. (B) Correlation between time from spinal anesthesia to delivery and umbilical arterial pH. The two variables were negatively correlated with adjusted $r = 0.57$ ($P < 0.001$). Low arterial pH values (< 7.10) were associated only with assignment to the ephedrine-only group and time from spinal anesthesia to delivery longer than 33 min. E = ephedrine; P = phenylephrine.

reported an 80–85% incidence of hypotension despite prophylactic 10- or 20-mg bolus doses of ephedrine. Only parturients randomized to receive the largest ephedrine bolus dose (30 mg) experienced a lower incidence of hypotension (35%), but this dose caused frequent reactive hypertension.

Our study confirms that hypotension remains a common complication during scheduled cesarean delivery performed with spinal anesthesia, despite prophylactic intravenous ephedrine infusion. In an attempt to ameliorate this problem, alternative vasopressors with enhanced vasoconstrictive properties have been studied. Prophylactic angiotensin II infusion performed better than prophylactic ephedrine infusion; however, it is

neither recommended nor available for clinical use in this circumstance.^{28,29} Pure α -agonist vasopressors initially were considered contraindicated in obstetrics, because early experimental studies reported a substantial decrease in uteroplacental blood flow linked to their vasoconstrictive properties.^{18,30,31} However, doses used in these studies were much higher than those needed clinically in humans, although they were appropriate to the species studied to restore spinal anesthesia-induced hypotension. In addition, a more recent experimental study suggested that pregnancy is associated with an attenuated uterine vascular response to phenylephrine.¹⁹ Clinical studies in women undergoing scheduled cesarean delivery have confirmed that small (40–100 μ g) bolus doses of phenylephrine used to counteract hypotension during epidural²⁰ or spinal anesthesia^{21–24} were effective and as safe as ephedrine bolus doses for the mother and the neonate.

Although treatment of hypotension with phenylephrine appears useful, administering it alone for prophylaxis has proved disappointing.⁵ Because rescue phenylephrine bolus doses appear effective when ephedrine alone fails to correct hypotension,^{4,25} we hypothesized that prophylactic infusion of the two drugs together should be more effective than ephedrine alone. We found that, compared with ephedrine alone, the ephedrine-phenylephrine combination decreased the incidence of hypotension by approximately 50%, abolished maternal tachycardia, decreased the frequency of nausea, and improved venous and arterial umbilical pH. The lack of significant difference between the E+P and E groups in SBP measurements (fig. 1), minimum SBP, and duration of hypotension (table 2), despite a favorable trend, probably reflects the prompt and effective treatment of hypotension with rescue ephedrine bolus doses in both groups. It is also noteworthy that the addition of phenylephrine to prophylactic ephedrine did not increase the risk of reactive hypertension (as shown by maximal SBP and percentage of SBP higher than 120% of baseline, table 2).

Ramanathan *et al.*²⁰ suggested that intravenous bolus doses of ephedrine and phenylephrine restored blood pressure similarly during epidural anesthesia for cesarean delivery by producing a comparable increase in preload only. However, Thomas *et al.*²⁴ found that, although ephedrine and phenylephrine restored blood pressure to comparable levels by causing similar increases in cardiac output, heart rate was lower with phenylephrine. As cardiac output is the product of heart rate and stroke volume, this suggests that phenylephrine restored a greater stroke volume than ephedrine. Because phenylephrine (but not ephedrine) is virtually devoid of β -inotropic effect, the better stroke volume produced by phenylephrine probably reflects a much better preload than with ephedrine, *i.e.*, a better control of venous pooling caused by venoconstriction. Further

studies are needed to specifically address these mechanisms.

One concern with phenylephrine is that it may cause bradycardia. However, this occurred frequently in only one study in the literature in which the median dose used was high (600 μg).²⁴ The bradycardia responded to atropine treatment and was unrelated to hypertensive response. Because the sensory block reached T2–T4 levels in the study patients, the investigators proposed cardiac sympathetic denervation as the most likely mechanism for the bradycardia. An ephedrine–phenylephrine combination should help prevent bradycardia in this circumstance, because the β -mimetic effect of ephedrine should counteract this tendency. Except in one instance, bradycardia was not observed in the E+P group in the current study, as reflected both in figure 2 and in table 2 (by minimum maternal heart rate). In contrast, the addition of phenylephrine completely abolished the tachycardia observed with prophylactic ephedrine alone (fig. 2). Thus, we believe the phenylephrine/ephedrine ratio we used is appropriate and would not recommend increasing it unless further studies demonstrated additional benefit. In addition to the lower incidence of hypotension and nausea in the E+P group, the lack of tachycardia is an important benefit of the combination in parturients because of their increased susceptibility to supraventricular tachycardia.³²

Apgar scores were similar in the groups and never less than 7, although the incidence of arterial $p\text{H}$ less than 7.20 was greater than desired. However, this is not new information. Several studies have reported a surprisingly high incidence of acidosis (not accompanied by neonatal depression) after spinal anesthesia for cesarean delivery.^{13,33,34} In addition, umbilical venous and arterial $p\text{H}$ values were significantly greater in the E+P group compared with the E group (table 3). This agrees with several clinical studies that have reported higher umbilical arterial $p\text{H}$ with phenylephrine compared with ephedrine.^{21,23,24} These findings are also consistent with the minimal, or lack of, change in uterine pulsatility index and umbilical pulsatility index reported in parturients after phenylephrine administration.^{22,24} Thomas *et al.*²⁴ noted that umbilical arterial $p\text{H}$ was normal even in three parturients who received a total dose of 1,000 μg phenylephrine ($p\text{H}$ values were 7.33, 7.30, and 7.25). Considered together, these results contradict the experimental data suggesting that phenylephrine dramatically decreases uteroplacental blood flow.^{18,35} As Rout *et al.*¹⁷ pointed out, most of the older experimental data were obtained in animals with nonhemochorial placentas and may not be directly relevant to humans.

In contrast to the lack of adverse neonatal effect with phenylephrine, many investigators have reported lower umbilical $p\text{H}$ values after prophylactic maternal ephedrine administration.^{7,10,12,15–17} This was most evident

when large ephedrine doses (≥ 50 mg administered intramuscularly or 3–4 mg/min administered intravenously) were used^{12,15} and when no crystalloid preload was administered.¹² Stepwise regression in our study confirmed a significant negative correlation between umbilical arterial $p\text{H}$ and total ephedrine dose. LaPorta *et al.*²³ showed that umbilical arterial $p\text{H}$ was negatively correlated with neonatal noradrenaline concentrations, which were much more likely to be high after ephedrine than after phenylephrine administration. They also demonstrated that high neonatal noradrenaline concentrations were related to direct fetal secretion likely induced by ephedrine transferred from the mother to the fetus.¹⁶ Therefore, it is possible that we might not have observed a better acid-base status in the E+P group, but rather a worse acid-base status in the E group because of a higher total ephedrine dose requirement. Another mechanism might be a prolonged period of decreased maternal cardiac output occurring before delivery. This is suggested by the correlation we found between the time from spinal anesthesia to delivery and both umbilical arterial and venous $p\text{H}$ (figs. 3A and 3B). Indeed, Robson *et al.*³³ found that umbilical arterial $p\text{H}$ correlated well with maternal cardiac output (but not with blood pressure itself). If, as previously discussed, the ephedrine–phenylephrine combination not only decreased the incidence of hypotension but also better preserved maternal cardiac output, this could explain why low venous (< 7.20) and arterial (< 7.10) $p\text{H}$ values in the current study were associated only with E-group assignment and prolonged time from spinal anesthesia to delivery.

We acknowledge that, despite a 50% decrease in the incidence of hypotension with our ephedrine–phenylephrine regimen, hypotension was still too frequent (37%). Figure 1 suggests that more sustained prophylaxis should be provided during the first 5 min after spinal anesthesia. This might be achieved either with a higher initial rate or an initial bolus of the combination, but with limitation of the total dose to avoid reactive hypertension. Alternatively, moderate volumes of a supplemental colloid preload might prove useful.^{27,36}

In summary, hypotension during spinal anesthesia for scheduled cesarean delivery remains a common complication despite prophylactic intravenous ephedrine infusion. We demonstrated that the addition of phenylephrine to an ephedrine infusion halved the incidence of hypotension, abolished tachycardia, and reduced nausea and vomiting. In addition, it was associated with higher venous and arterial umbilical $p\text{H}$ values in healthy patients with uncomplicated pregnancies. Although neonatal benefit might be even more pronounced with this drug combination in situations with decreased fetal reserve, additional studies are needed to specifically address this issue.

References

- Datta S, Milton HA, Ostheimer GW, Weiss JB: Method of ephedrine administration and nausea and hypotension during spinal anesthesia for cesarean section. *ANESTHESIOLOGY* 1982; 56:68-70
- Kang YG, Abouleish E, Caritis S: Prophylactic intravenous ephedrine infusion during spinal anesthesia for cesarean section. *Anesth Analg* 1982; 61: 839-42
- Tong C, Eisenach JC: The vascular mechanism of ephedrine's beneficial effect on uterine perfusion during pregnancy. *ANESTHESIOLOGY* 1992; 76:792-8
- Morgan P: The role of vasopressors in the management of hypotension induced by spinal and epidural anaesthesia. *Can J Anaesth* 1994; 41:404-13
- Hall PA, Bennett A, Wilkes MP, Lewis M: Spinal anaesthesia for caesarean section: Comparison of infusions of phenylephrine and ephedrine. *Br J Anaesth* 1994; 73:471-4
- Jackson R, Reid JA, Thorburn J: Volume preloading is not essential to prevent spinal-induced hypotension at caesarean section. *Br J Anaesth* 1995; 75:262-5
- Chan WS, Irwin MG, Tong WN, Lam YH: Prevention of hypotension during spinal anaesthesia for caesarean section: Ephedrine infusion versus fluid preload. *Anaesthesia* 1997; 52:908-13
- Husaini SW, Russell IF: Volume preload: lack of effect in the prevention of spinal-induced hypotension at caesarean section. *Int J Obstet Anesth* 1998; 7:76-81
- Olsen KS, Feilberg VL, Hansen CL, Rudkjoberg O, Pedersen T, Kyst A: Prevention of hypotension during spinal anaesthesia for caesarean section. *Int J Obstet Anesth* 1994; 3:20-4
- Shearer VE, Ramin SM, Wallace DH, Dax JS, Gilstrap LC 3rd: Fetal effects of prophylactic ephedrine and maternal hypotension during regional anaesthesia for caesarean section. *J Maternal Fetal Med* 1996; 5:79-84
- King SW, Rosen MA: Prophylactic ephedrine and hypotension associated with spinal anaesthesia for caesarean delivery. *Int J Obstet Anesth* 1998; 7:18-22
- Morgan D, Philip J, Sharma S, Gottumukkala V, Perez B, Wiley J: A neonatal outcome with ephedrine infusions with or without preloading during spinal anaesthesia for caesarean section (abstract). *ANESTHESIOLOGY* 2000; 92(suppl):A5
- Ngan Kee WD, Khaw KS, Lee BB, Lau TK, Gin T: A dose-response study of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anaesthesia for caesarean delivery. *Anesth Analg* 2000; 90:1390-5
- Tsen LC, Boosalis P, Segal S, Datta S, Bader AM: Hemodynamic effects of simultaneous administration of intravenous ephedrine and spinal anaesthesia for caesarean delivery. *J Clin Anesth* 2000; 12:378-82
- Rolbin SH, Cole AF, Hew EM, Pollard A, Virgint S: Prophylactic intramuscular ephedrine before epidural anaesthesia for caesarean section: Efficacy and actions on the foetus and newborn. *Can Anaesth Soc J* 1982; 29:148-53
- Hughes SC, Ward MG, Levinson G, Shnider SM, Wright RG, Gruenke LD, Craig JC: Placental transfer of ephedrine does not affect neonatal outcome. *ANESTHESIOLOGY* 1985; 63:217-9
- Rout CC, Rocke DA, Brijball R, Koovarjee RV: Prophylactic intramuscular ephedrine prior to caesarean section. *Anaesth Intensive Care* 1992; 20:448-52
- Greiss FC, Van Wilkes D: Effects of sympathomimetic drugs and angiotensin on the uterine vascular bed. *Obstet Gynecol* 1964; 23:925-30
- Magness RR, Rosenfeld CR: Systemic and uterine responses to alpha-adrenergic stimulation in pregnant and non-pregnant ewes. *Am J Obstet Gynecol* 1986; 155:897-904
- Ramanathan S, Grant GJ: Vasopressor therapy for hypotension due to epidural anaesthesia for caesarean section. *Acta Anaesthesiol Scand* 1988; 32:559-65
- Moran DH, Perillo M, Bader AM, Datta S: Phenylephrine in the prevention of hypotension following spinal anaesthesia for caesarean delivery. *J Clin Anesth* 1991; 3:301-5
- Alahuhta S, Rasanen J, Jouppila P, Jouppila R, Hollmen AI: Ephedrine and phenylephrine for avoiding maternal hypotension due to spinal anaesthesia for caesarean section. *Int J Obstet Anesth* 1992; 1:129-34
- LaPorta RF, Arthur GR, Datta S: Phenylephrine in treating maternal hypotension due to spinal anaesthesia for caesarean delivery: Effects on neonatal catecholamine concentrations, acid base status and Apgar scores. *Acta Anaesthesiol Scand* 1995; 39:901-5
- Thomas DG, Robson SC, Redfern N, Hughes D, Boys RJ: Randomized trial of bolus of phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for caesarean section. *Br J Anaesth* 1996; 76:61-5
- Taylor JC, Tunstall ME: Dosage of phenylephrine in spinal anaesthesia for caesarean section. *Anaesthesia* 1991; 46:314-6
- Riley ET, Cohen SE, Macario A, Desai JB, Ratner EF: Spinal versus epidural anaesthesia for caesarean section: A comparison of time efficiency, costs, charges, and complications. *Anesth Analg* 1995; 80:709-12
- Ueyama H, He YL, Tanigami H, Mashimo T, Yoshiya I: Effects of crystalloid and colloid preload on blood volume in the parturient undergoing spinal anaesthesia for elective caesarean section. *ANESTHESIOLOGY* 1999; 91:1571-6
- Ramin SM, Ramin KD, Cox K, Magness RR, Shearer VE, Gant NF: Comparison of prophylactic angiotensin II versus ephedrine infusion for prevention of maternal hypotension during spinal anaesthesia. *Am J Obstet Gynecol* 1994; 171:737-9
- Vincent RD, Werhan CF, Norman PF, Shih GH, Chestnut DH, Ray T, Ross EL, Bofill JA, Shaw DB: Prophylactic angiotensin II infusion during spinal anaesthesia for elective caesarean delivery. *ANESTHESIOLOGY* 1998; 88:1475-9
- James FM, Greiss FC, Kemp RA: An evaluation of vasopressor therapy for maternal hypotension during spinal anaesthesia. *ANESTHESIOLOGY* 1970; 33:25-34
- Ralston DH, Shnider SM, DeLorimier AA: Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. *ANESTHESIOLOGY* 1974; 40:354-70
- Gajraj NM, Wallace DH, Pace NA: Supraventricular tachycardia in a parturient under spinal anaesthesia. *Reg Anesth* 1993; 18:261-3
- Robson SC, Boys RJ, Rodeck C, Morgan B: Maternal and fetal haemodynamic effects of spinal and extradural anaesthesia for elective caesarean section. *Br J Anaesth* 1992; 68:54-9
- Roberts SW, Leveno KJ, Sidawi JE, Lucas MJ, Kelly MA: Fetal acidemia associated with regional anaesthesia for elective caesarean delivery. *Obstet Gynecol* 1995; 85:79-83
- McGrath JM, Chestnut DH, Vincent RD, DeBruyn CS, Atkins BL, Poduska DJ, Chatterjee P: Ephedrine remains the vasopressor of choice for treatment of hypotension during ritodrine infusion and epidural anaesthesia. *ANESTHESIOLOGY* 1994; 80:1073-81
- Wennberg E, Frid I, Haljamae H, Noren H: Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural caesarean section. *Br J Anaesth* 1992; 69:13-8