Randomized Double-blinded Comparison of Norepinephrine and Phenylephrine for Maintenance of Blood Pressure during Spinal Anesthesia for Cesarean Delivery

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ABSTRACT

Background: During spinal anesthesia for cesarean delivery, phenylephrine can cause reflexive decreases in maternal heart rate and cardiac output. Norepinephrine has weak β-adrenergic receptor agonist activity in addition to potent α-adrenergic receptor activity and therefore may be suitable for maintaining blood pressure with less negative effects on heart rate and cardiac output compared with phenylephrine.

Methods: In a randomized, double-blinded study, 104 healthy patients having cesarean delivery under spinal anesthesia were randomized to have systolic blood pressure maintained with a computer-controlled infusion of norepinephrine 5 μg/ml or phenylephrine 100 μg/ml. The primary outcome compared was cardiac output. Blood pressure heart rate and neonatal outcome were also compared.

Results: Normalized cardiac output 5 min after induction was greater in the norepinephrine group *versus* the phenylephrine group (median 102.7% [interquartile range, 94.3 to 116.7%] *versus* 93.8% [85.0 to 103.1%], $P = 0.004$, median difference 9.8%, 95% CI of difference between medians 2.8 to 16.1%). From induction until uterine incision, for norepinephrine *versus* phenylephrine, systolic blood pressure and stroke volume were similar, heart rate and cardiac output were greater, systemic vascular resistance was lower, and the incidence of bradycardia was smaller. Neonatal outcome was similar between groups.

Conclusions: When given by computer-controlled infusion during spinal anesthesia for cesarean delivery, norepinephrine was effective for maintaining blood pressure and was associated with greater heart rate and cardiac output compared with phenylephrine. Further work would be of interest to confirm the safety and efficacy of norepinephrine as a vasopressor in obstetric patients. **(ANESTHESIOLOGY 2015; 122:736-45)**

PHENYLEPHRINE is commonly used to maintain blood pressure during spinal anesthesia for cesarean delivery.[1,2] However, because phenylephrine is a potent α-adrenergic receptor agonist without β-adrenergic receptor activity at usual clinical doses, its use is often associated with a dose-related reflexive slowing of maternal heart rate (HR) and a corresponding decrease in cardiac output (CO).[3–5] Although the clinical significance of these decreases in HR and CO in healthy patients with unstressed fetuses is unknown, concern has been expressed that there may be potential for harm in the presence of a compromised fetus.[3] Therefore, investigation of alternative vasopressors with less pronounced reflexive negative chronotropic effects is of interest.

Norepinephrine has pharmacologic properties that suggest it may be a useful alternative to phenylephrine. Norepinephrine is a potent α-adrenergic receptor agonist, but unlike phenylephrine, it is also a relatively weak agonist at β-adrenergic receptors. We postulated that norepinephrine might therefore

What We Already Know about This Topic

- Although norepinephrine has theoretical advantages over phenylephrine to treat spinal anesthesia–induced hypotension in obstetric patients, it has not been assessed in this setting

What This Article Tells Us That Is New

- In a randomized study of 104 healthy patients undergoing cesarean delivery under spinal anesthesia, maternal blood pressure and Apgar scores of neonates were similar whether norepinephrine or phenylephrine was administered
- Maternal cardiac output and heart rate were greater in women treated with norepinephrine compared with that in women treated with phenylephrine, but further work is needed to assess safety and efficacy of norepinephrine in this setting

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be an effective vasopressor for maintaining blood pressure during spinal anesthesia with less tendency to decrease HR and CO compared with phenylephrine. Although treatment of hypotension during spinal anesthesia is listed by the manufacturer as an indication for the use of norepinephrine, there is limited information available for its use for this purpose in the literature and few reports of its use in obstetric patients.[6]

The aim of this randomized, double-blinded study was to compare computer-controlled infusions of phenylephrine and norepinephrine titrated to maintain blood pressure in parturients having spinal anesthesia for elective cesarean delivery. We hypothesized that an infusion of norepinephrine would be effective for maintaining blood pressure but with greater HR and CO compared with phenylephrine. Secondary outcomes assessed included neonatal outcome and assessment of umbilical cord blood metabolic markers.

Materials and Methods

Approval was obtained from the Joint Chinese University of Hong Kong, New Territories East Cluster Clinical Research Ethics Committee, Shatin, Hong Kong, China, and a Certificate for Clinical Trial/Medicinal Test was obtained from the Department of Health of the Government of the Hong Kong Special Administrative Region, Hong Kong, China, before commencing the study. The study protocol was registered in the Centre of Clinical Trials Clinical Registry of the Chinese University of Hong Kong, Shatin, Hong Kong, China (reference no. CUHK_CCT00315) and in the Chinese Clinical Trial Registry (registration no. ChiCTR-TRC-12002135) with the title *Randomized Evaluative Study of Phenylephrine Or Norepinephrine for maintenance of blood pressure during spinal anesthesia for cesarean Delivery: The RESPOND study*. All patients gave written informed consent to participate.

We enrolled 104 patients who matched the following inclusion criteria: American Society of Anesthesiologists physical status 1 to 2, singleton, term pregnancy, and scheduled for elective cesarean delivery under routine spinal anesthesia. Exclusion criteria were as follows: onset of labor, known fetal abnormality, hypertension, cardiovascular or cerebrovascular disease, renal impairment, allergy to any study medication, weight less than 50 kg or more than 100 kg, height less than 140 cm or more than 180 cm, age less than 18 yr, patients taking monoamine oxidase inhibitors or tricyclic antidepressants, and presence of mesenteric or peripheral vascular thrombosis.

Patients were fasted overnight and were given routine antacid prophylaxis. On arrival in the operating room, they were positioned on the operating table in the supine position with left lateral tilt and routine monitors were attached (Infinity C500; Dräger Medical AG & Co. KG, Germany). After a brief settling period, baseline hemodynamic measurements were made. HR was recorded using pulse oximetry and electrocardiography, and blood pressure was recorded using an automated noninvasive device that was cycled every 1 to 2 min until three consecutive measurements of systolic blood pressure were recorded with a difference of not more than 10%. The mean values of blood pressure and HR at these times were calculated and defined as baseline values. We then measured baseline CO noninvasively using suprasternal Doppler (USCOM 1A Cardiac Output Monitor; USCOM Ltd., Australia) as we have previously described.[7] Values for stroke volume (SV) and systemic vascular resistance (SVR) were also derived by the apparatus. All measurements were made by the same experienced operator (S.W.Y.L.) who was blinded to group assignment and were repeated three times with the mean of the three measurements recorded as the baseline value.

A large-bore intravenous cannula was then inserted into a forearm vein under local anesthesia, but no prehydration was given. Patients were positioned in the right lateral position, and spinal anesthesia was administered using full aseptic precautions. After skin infiltration with lidocaine 1% (w/v), a 25-gauge pencil-point spinal needle was inserted through an introducer needle at what was estimated to be the L3 to L4 or L4 to L5 vertebral interspace. After confirmation of free flow of cerebrospinal fluid, 2.2 ml of hyperbaric bupivacaine 0.5% (w/v) and 15 μg fentanyl were injected intrathecally, and the patient was returned to the tilted supine position. At the start of intrathecal injection, rapid intravenous cohydration of lactated Ringer's solution was commenced. Infusion bags were suspended approximately 1.5 m above the mid-point of the top surface of the operating table, and the fluid was administered through a wide-bore administration set with the clamp fully opened. Cohydration was continued to a maximum of 2 l after which the flow was reduced to a slow maintenance rate.

Infusion of the study drug was started at the same time as cohydration. An investigator (F.F.N.) who was not involved in subsequent patient care or assessment opened the topmost of 104 opaque sequentially numbered envelopes that had been prepared by a member of the secretarial staff. Each envelope contained a randomization code corresponding to one of the study drugs. The codes had been prepared using an on-line random number generator* that had been set to use a closed-sequence algorithm to ensure equal numbers in each group. According to the randomization code, a solution of either norepinephrine 5 μg/ml (norepinephrine group) or phenylephrine 100 μg/ml (phenylephrine group) was selected. The concentration of phenylephrine was our standard preparation, and the concentration of norepinephrine was chosen as that estimated to be approximately equipotent based on the results of previous comparative studies on human saphenous vein,[8] adjusted to a round number for ease of preparation. The drugs were prepared by careful dilution in 5% dextrose solution in 50-ml syringes that were labelled "study drug" and were administered through fine-bore tubing connected to a three-way stopcock that was attached directly to the intravenous catheter. The randomization code was not revealed until after recruitment of the final patient in the study.

* Available at: http://www.psychicscience.org/random.aspx. Accessed January 9, 2012.

From the start of intrathecal injection until delivery, the vasopressor infusion was regulated using a computer-controlled closed-loop feedback system that we have previously described.[7,9,10] The infusion was initially commenced at a fixed rate of 30 ml/h. After the completion of the first blood pressure measurement after spinal injection, the infusion was regulated to maintain systolic blood pressure according to the following algorithm:

$$\text{Infusion rate}\,(\text{ml/h}) = (10 - \text{error}\%) \times 3 \quad (1)$$

where error% = (measured systolic blood pressure − baseline systolic blood pressure)/baseline systolic blood pressure × 100). The infusion rate was constrained to be within the limits 0 to 60 ml/h (0 to 5 μg/min of norepinephrine or 0 to 100 μg/min of phenylephrine). The computer program sampled hemodynamic parameters at 1-s intervals and defaulted to an infusion rate of 0 ml/h during any periods when HR was less than 50 beats/min. The total volume of vasopressor solution given up to the time of uterine incision was recorded.

The noninvasive blood pressure monitor was started 1 min after intrathecal injection, and the automatic cycling time was set to 1 min until delivery. The actual times of starting and completing measurements were determined by the internal algorithm of the monitor which is preset by the manufacturer. HR was recorded at the time of completion of each blood pressure measurement. CO was measured at 5-min intervals until delivery according to a stopwatch that was started at the time of intrathecal injection. The incidences of hypotension (defined as systolic blood pressure <80% of baseline), hypertension (defined as systolic blood pressure >120% of baseline), and bradycardia (defined as HR <60 beats/min) were recorded. Episodes of bradycardia were managed expectantly without administration of anticholinergic drugs.

The highest level of sensory anesthesia assessed using ice was recorded 5 min after intrathecal injection for the purpose of comparison. Further assessments were made as clinically indicated but were not recorded for analysis. Surgery was allowed to commence when the attending anesthesiologist considered the block was adequate. Supplemental oxygen was not given unless the pulse oximeter reading decreased below 95%.

After delivery, Apgar scores were assessed by a midwife 1 and 5 min after delivery. Samples of umbilical arterial (UA) and umbilical venous (UV) blood were collected from a double-clamped segment of umbilical cord. Immediate measurement was made of blood gases using a Rapid Point 400 analyzer (Bayer Diagnostics Mfg [Sudbury] Ltd., United Kingdom), oxygen content with correction for 70% fetal hemoglobin using an IL 682 Co-Oximeter (Instrumentation Laboratory, USA) and plasma concentrations of lactate and glucose using the Vitros DT60 II Chemistry System (Ortho-Clinical Diagnostics, USA). In addition, blood samples were placed in ice for measurement of plasma concentrations of epinephrine and norepinephrine using methods described in the appendix.

Statistical Analysis

The primary outcome measurement compared was defined as CO. Sample size calculation was based on data from our previous published[7] and unpublished data (personal database of hemodynamic data from obstetric patients, Warwick D. Ngan Kee M.B.Ch.B., M.D., F.A.N.Z.C.A., F.H.K.A.M., Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China). We calculated that a sample size of 47 patients per group would have greater than 90% power to detect a 20% difference in CO between groups 5 min after spinal injection with an α error probability of 0.05 assuming an anticipated mean value in the phenylephrine group of 6.2 l/min and SD of 1.8 l/min. To account for potential dropouts, the sample size was increased by 5% giving a final sample size of 52 patients per group.

Univariate intergroup data were tested for normality using the Kolmogorov–Smirnov test and compared using Student *t* test or the Mann–Whitney U test as appropriate. Nominal data were compared using the chi-square test or Fisher exact test. Serial hemodynamic data were compared between groups using a summary measures technique.[11,12] For systolic blood pressure and HR, because the noninvasive blood pressure monitor took variable times to complete measurements and cycle, data were grouped according to the chronological recording order with the apparatus set to a 1-min cycle time. For CO, SV, and SVR, data measured at 5-min real-time intervals were analyzed for the first 20 min which was greatest time point for which data were available for all patients; these values were normalized to percentage of baseline values using the formula:

$$\text{Normalized value} = \frac{\text{Measured value}}{\text{Baseline value}} \times 100\% \quad (2)$$

The area under the curve for values plotted against time were calculated using the trapezium rule.[11,12] For systolic blood pressure and HR, because the number of data points recorded varied among patients, values for area under the curve for each patient were divided by the number of data points recorded to give standardized values.[12] Values for area under the curve and standardized area under the curve were then compared between groups using the Mann–Whitney U test.

Analyses were performed using Microsoft Excel 2010 (Microsoft Corporation, USA), IBM SPSS Statistics version 20 (IBM SPSS Inc., USA), and Confidence Interval Analysis 2.2.0 (Trevor Bryant, University of Southampton, United Kingdom). Values of *P* less than 0.05 were considered statistically significant.

Results

Patient recruitment and flow are shown in figure 1. One hundred four patients entered the study, and after exclusions, data were analyzed from 49 patients in the norepinephrine group and 52 patients in the phenylephrine group. Data from all patients were analyzed according to

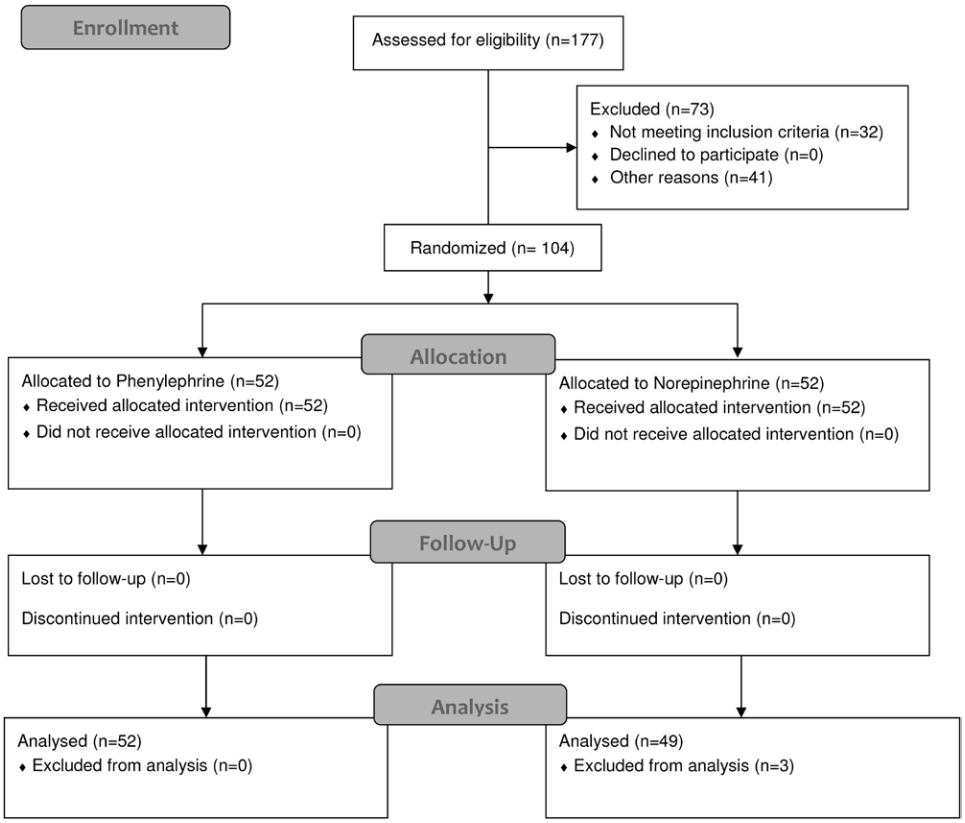

Fig. 1. CONSORT diagram showing patient recruitment and flow.

their assigned groups. Patient characteristics are shown in table 1. One patient in the norepinephrine group required supplemental oxygen. Because the noninvasive blood pressure apparatus took a varying time for each measurement and surgical time varied among patients, a variable number of measurements of blood pressure and HR were recorded for each patient (norepinephrine group: median 14 [range, 10 to 34] and phenylephrine group: median 13 [range, 9 to 26]). For measurements of CO, which were timed according to a stopwatch, a minimum of four recordings after induction of anesthesia were obtained from all patients. Because of equipment failure, umbilical cord blood gases could not be measured for one patient in the norepinephrine group and oxygen content could not be measured for three patients in the phenylephrine group and three patients in the norepinephrine group. In the norepinephrine group, insufficient blood was obtained for the following measurements: UA epinephrine (two patients), UV epinephrine (one patient), UA norepinephrine (two patients), and UV norepinephrine (one patient). In the phenylephrine group, insufficient umbilical cord blood was obtained for the following measurements: UA epinephrine (five patients), UV epinephrine (one patient), UA norepinephrine (four patients), and UV norepinephrine (one patient).

Table 1. Patient Characteristics and Surgical Times

	Phenylephrine Group (n = 52)	Norepinephrine Group (n = 49)
Age (yr)	33.9 (3.9)	33.1 (4.1)
Weight (kg)	68.3 (6.9)	67.9 (9.2)
Height (cm)	158 (6.1)	157 (5.6)
Block height (dermatome)	T4 [T3–T5]	T3.5 [T3–T5]
Induction-to-delivery interval (min)	28.5 [26.2–34.2]	29.4 [26.1–34.1]
Incision-to-delivery interval (min)	9.6 [6.7–12.6]	9.1 [7.1–12.2]
Uterine incision-to-delivery interval (s)	84 [57–109]	92 [61–129]

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

Normalized CO at 5 min (primary outcome) was greater in the norepinephrine group compared with that in the phenylephrine group (median 102.7% [interquartile range, 94.3 to 116.7%] *versus* 93.8% [85.0 to 103.1%], $P = 0.004$, median difference 9.8%, 95% CI of difference between medians 2.8 to 16.1%). Changes in systolic blood pressure and HR over time are shown in figure 2; systolic blood pressure was similar between groups ($P = 0.36$), whereas HR was greater in the norepinephrine group compared with that in the phenylephrine group ($P = 0.039$). Changes in CO, SV, and SVR over time are shown in figure 3; CO was greater ($P < 0.001$) and SVR was lower ($P < 0.001$) in the norepinephrine group compared with that in the phenylephrine group, but there was no difference in SV ($P = 0.44$).

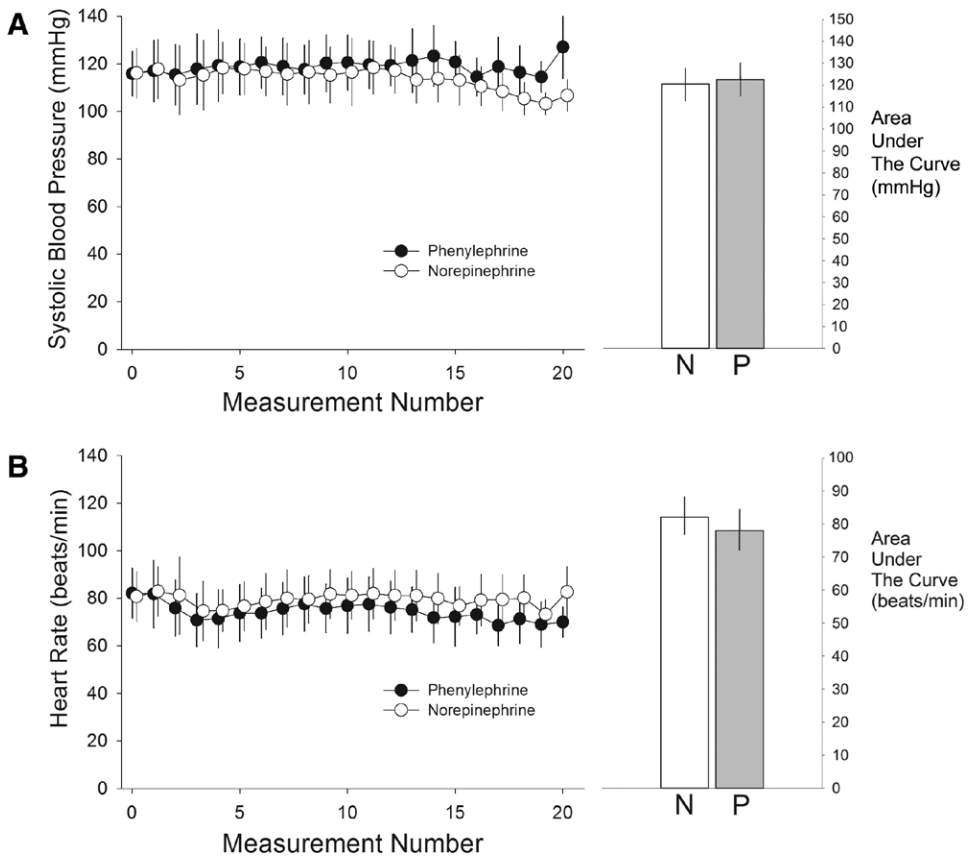

Fig. 2. Serial changes in systolic blood pressure (*A*) and heart rate (*B*). On the left side of the panels, data are serial values for the first 20 measurements shown as mean and SD. Because the noninvasive blood pressure monitor took a variable time to start and complete each blood pressure measurement, tick values on the horizontal axis represent the sequential number of each measurement made with the monitor set to an automatic 1-min cycling time rather than exact chronological time. On the right side of the panels, *bars* show the area under the curve for the two groups (N = norepinephrine and P = phenylephrine) standardized for each patient by dividing by the number of data points recorded and shown as median and interquartile range. Comparison of the calculated values for standardized area under the curve showed that systolic blood pressure was similar between groups ($P = 0.36$), but heart rate was greater over time in the norepinephrine group *versus* the phenylephrine group ($P = 0.039$).

The incidence of bradycardia, defined as an HR less than 60 beats/min, was lower in the norepinephrine group (18.4%) compared with that in the phenylephrine group (55.8%, $P < 0.001$). The rate of vasopressor administration was greater in the norepinephrine group (median 0.47 ml/min [interquartile range [0.39 to 0.58 ml/min]) compared with that in the phenylephrine group (39.1 ml/min [32.7 to 45.4 ml/min], $P = 0.002$). Three patients (6.1%) in the norepinephrine group and two patients (3.8%) in the phenylephrine group had nausea or vomiting ($P = 0.67$).

Neonatal outcome is summarized in table 2. All Apgar scores at 1 and 5 min were greater than 7, and no patient had UA pH less than 7.2. UA P_{O_2} was less than the lower limit of detection of the blood gas analyzer (10 mmHg) in two patients in the norepinephrine group and five patients in the phenylephrine group, and UV P_{O_2} was less than the lower limit of detection of the blood gas analyzer in one patient in the phenylephrine group; for analysis, these data values were entered as constant values equal to the lower limit of detection divided by $\sqrt{2}$,[13] and the data were analyzed by ranks. UV pH and UV oxygen content were higher in the norepinephrine group compared with that in the phenylephrine group. All other parameters were similar between groups.

Umbilical cord plasma concentrations of glucose, lactate, epinephrine, and norepinephrine are shown in table 3. Plasma concentrations were below the lower limit of detection (25 pg/ml) for the following: norepinephrine group: UA epinephrine (2 patients) and UV epinephrine (14 patients); phenylephrine group: UA epinephrine (2 patients) and UV epinephrine (14 patients). For analysis, data for these cases were entered as constant values equal to the lower limit of detection divided by $\sqrt{2}$,[13] and the data were analyzed by ranks. UA plasma concentrations of epinephrine and UA and UV plasma concentrations of norepinephrine were lower in the norepinephrine group compared with that in the phenylephrine group. UA and UV plasma concentrations of glucose were greater in the norepinephrine group compared with that in the phenylephrine group.

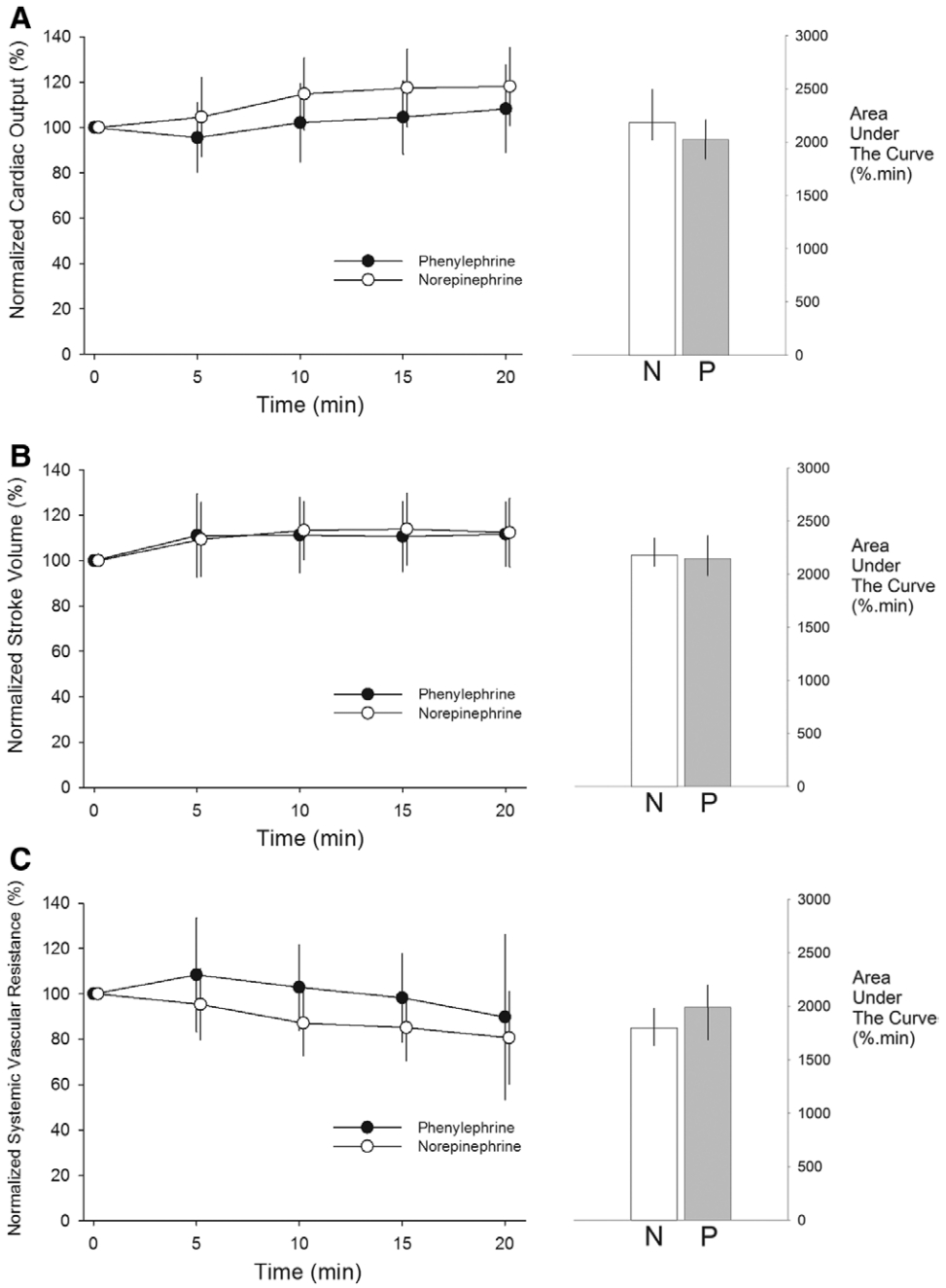

Fig. 3. Serial changes in cardiac output (*A*), stroke volume (*B*), and systemic vascular resistance (*C*). On the left side of the panels, data are serial values for the first 20 min after induction of spinal anesthesia normalized to percentage of baseline values. On the right side of the panels, *bars* show the area under the curve for the two groups (N = norepinephrine and P = phenylephrine). Comparison of the calculated values for area under the curve showed that cardiac output was greater over time ($P < 0.001$) and systemic vascular resistance was lower over time ($P < 0.001$) in the norepinephrine group compared with that in the phenylephrine group, but there was no difference in stroke volume ($P = 0.44$). Values are shown as median and interquartile range.

Discussion

The results of our study show that compared with phenylephrine, norepinephrine had similar efficacy for maintaining blood pressure during spinal anesthesia for cesarean delivery but was associated with greater HR and CO and lower SVR. These findings confirm our postulate that the use of a drug such as norepinephrine that has mild β-adrenergic receptor activity in addition to potent α-adrenergic receptor activity would exhibit similar vasopressor efficacy as phenylephrine but with a reduction in the undesirable negative chronotropic effects.

The typical hemodynamic response to spinal anesthesia in parturients is a decrease in SVR with a compensatory increase in HR and CO; thus, immediate treatment with an

Table 2. Neonatal Outcome

	Norepinephrine Group	Phenylephrine Group	*P* Value
Birth weight (kg)	3.11 [2.85–3.37]	3.19 [3.04–3.36]	0.37
Apgar score at 1 min <8	0	0	
Apgar score at 5 min <8	0	0	
Umbilical arterial blood gases			
pH	7.30 [7.28–7.33]	7.29 [7.28–7.32]	0.45
P_{CO_2} (mmHg)	50 [48–56]	52 [48–56]	0.77
P_{O_2} (mmHg)	15 [13–18]	14 [11–16]	0.20
Base excess (mmol/l)	−2.0 [−3.7 to −1.0]	−2.4 [−4.2 to −0.8]	0.87
Oxygen content (ml/dl)	6.0 [4.4–7.7]	5.2 [3.8–7.0]	0.29
Umbilical venous blood gases			
pH	7.35 [7.34–7.37]	7.34 [7.32–7.36]	0.031
P_{CO_2} (mmHg)	41 [38–43]	41 [38–45]	0.69
P_{O_2} (mmHg)	27 [23–30]	26 [23–28]	0.23
Base excess (mmol/l)	−3.2 [−4.1 to −2.0]	−3.5 [−5.6 to −2.4]	0.06
Oxygen content (ml/dl	12.7 [11.3–14.4]	11.8 [9.6–13.7]	0.047

Values are median [interquartile range] or number.

Table 3. Umbilical Cord Plasma Concentrations of Epinephrine, Norepinephrine, Glucose, and Lactate

	Phenylephrine Group	Norepinephrine Group	*P* Value
Umbilical arterial			
Epinephrine (pg/ml)	400 [227–700]	281 [78–491]	0.042
Norepinephrine (pg/ml)	2,178 [1,403–3,921]	1,756 [1,048–2,435]	0.035
Glucose (mg/dl)	46 [43–52]	53 [48–60]	<0.001
Lactate (mmol/l)	1.8 [1.6–2.0]	2.0 [1.7–2.4]	0.088
Umbilical venous			
Epinephrine (pg/ml)	40 [18–73]	23 [18–63]	0.16
Norepinephrine (pg/ml)	457 [281–647]	347 [225–486]	0.031
Glucose (mg/dl)	51 [44–56]	56 [51–62]	<0.001
Lactate (mmol/l)	1.8 [1.6–2.0]	2.0 [1.6–2.4]	0.33

Values are median [interquartile range].

α-adrenergic agonist is appropriate and recommended.[14] In this context, of available drugs, phenylephrine has become the agent most commonly recommended[14] although alternatives such as metaraminol are also effective.[15] Previously, we have shown that titrating phenylephrine to maintain maternal blood pressure near baseline values can reduce the incidence of maternal symptoms such as nausea and vomiting.[16] However, a drawback of the use of pure α-adrenergic drugs such as phenylephrine is that they have a dose-related tendency to decrease HR and CO, which can occur even without marked increases in blood pressure above baseline.[16] Concern has been expressed that this decrease in CO may adversely affect uteroplacental perfusion.[3] In this respect, a drug such as norepinephrine may potentially be advantageous. Norepinephrine has both direct positive chronotropic and reflexive negative chronotropic actions with the overall effect on HR considered to be approximately neutral.[17]

In our study, because SV was similar between groups, the greater CO in the norepinephrine group was primarily related to greater HR. The latter can most likely be attributed to the positive chronotropic effects of norepinephrine. However, it is possible that a positive effect on venous return may also have contributed. In nonobstetric subjects, it has been shown that pure α-adrenergic agonists can increase venous return by constricting capacitance vessels, but this may be opposed by an increase in venous resistance which can reduce venous return.[18,19] However, veins also have β-adrenergic receptors, and norepinephrine has been demonstrated to constrict capacitance vessels without an increase in venous resistance.[18,20] More work is required to determine whether venous return is greater during administration of norepinephrine compared with phenylephrine under conditions of spinal anesthesia in parturients. This may be particularly relevant for the occasional patient in whom bradycardia accompanies hypotension. In this situation, use of a drug such as norepinephrine that has positive effects on HR and venous return may be more appropriate than phenylephrine.

We found that blood pressure was maintained similarly in both groups, but in the norepinephrine group, this was associated with greater CO and lower SVR. Theoretically, this may be potentially more favorable for maintaining perfusion in the uteroplacental and other peripheral vascular beds. Interestingly, UV pH and UV oxygen content were greater in the norepinephrine group which possibly may

relate to greater placental blood flow and oxygen delivery in the norepinephrine group. However, the differences were small, umbilical cord blood gases were not the primary outcome of the study, and the use of multiple comparisons gives rise to the possibility of type I statistical error. Further work is required to confirm this observation and to determine whether norepinephrine may have any clinical advantage, for example, in patients with preeclampsia or in other conditions in which uteroplacental circulation may be compromised. Of note, we have previously observed greater umbilical cord blood P_{O_2} when ephedrine was used *versus* phenylephrine in both elective[21,22] and nonelective cesarean delivery[23] which may reflect a similar mechanism.

To our knowledge, this study is the first formal evaluation of norepinephrine as a vasopressor in obstetric patients. More commonly, norepinephrine is used in an intensive care setting, for example, in the treatment of patients with septic shock. In this context, it is noteworthy that phenylephrine is usually considered a second-line agent because of concerns that it increases blood pressure solely by vasoconstriction with a concomitant potential to decrease CO.[24–26] It has been reported that when phenylephrine is used to treat patients with septic shock, it decreases HR, decreases hepatosplanchnic perfusion, and impairs renal function compared with norepinephrine.[27,28] These findings are consistent with experimental work showing that regional and organ blood flow are better preserved with the use of norepinephrine compared with phenylephrine.[19] However, it is unknown whether these issues are relevant in the context of obstetric patients undergoing spinal anesthesia.

Umbilical arterial and UV plasma concentrations of norepinephrine and UA plasma concentration of norepinephrine were lower in the norepinephrine group than in the phenylephrine group. Because catecholamines are not thought to readily cross the placenta,[29] these findings probably reflect differences in fetal catecholamine production. Fetal catecholamine levels have been shown to be greater with increased stress during delivery and fetal asphyxia,[29,30] and an inverse correlation has been shown between umbilical blood catecholamine concentrations and P_{O_2}.[31] In our study, lower umbilical plasma catecholamine concentrations together with greater UV pH and oxygen content in the norepinephrine group suggest the possibility of decreased fetal stress in this group compared with the phenylephrine group which could be related to greater uteroplacental oxygen delivery. However, it should be noted that differences observed in our study were small, and the clinical significance of these findings in our low-risk patients is unclear.

Umbilical arterial and UV plasma glucose concentrations were greater in the norepinephrine group compared with that in the phenylephrine group. Because this was not associated with a difference in umbilical blood lactate concentration, pH, or base excess, stimulation of fetal metabolism as is thought to occur with ephedrine[22] is unlikely. It is possible that the higher umbilical blood concentrations of glucose in the norepinephrine group were the result of increased maternal glucose concentration and thus increased placental transfer that may have arisen from a stress hormone effect in parturients who received norepinephrine infusions.[32] However, we did not measure maternal plasma concentrations of glucose to confirm this suggestion.

We compared norepinephrine at a concentration of 5 μg/ml *versus* phenylephrine at a concentration of 100 μg/ml according to our estimate of a potency ratio of 20:1; this ratio has been used in previous clinical comparisons of norepinephrine and phenylephrine.[33,34] However, we found that the median infusion rate required to maintain blood pressure was greater in the norepinephrine group. This suggests that the true potency ratio for norepinephrine:phenylephrine for maintaining blood pressure under the conditions of our study is probably less than 20:1. Of note, this ratio relates to efficacy for maintaining blood pressure, which is affected by both CO and SVR. Our initial estimate of potency was based on previously reported work by Sjöberg *et al.*[8] who compared the effects of norepinephrine and phenylephrine according to the drugs' vasoconstrictor activity alone. Further work is required to determine the relative potencies of norepinephrine and phenylephrine used to maintain blood pressure in obstetric patients.

We measured CO using the technique of suprasternal Doppler. This technique has been shown to have good repeatability and also to be reliable in younger patients.[35] However, a disadvantage of the technique is that it depends on an estimate of aortic valve cross-sectional area that is determined using an algorithm based on patients' height. This introduces potential for systematic error in the derivation of absolute values although the ability to track trends is not affected.[35] We accounted for this in our analysis by normalizing all CO measurements and related derived parameters to percentage of baseline values.

Finally, we administered both vasopressor drugs by closed-loop computer-controlled infusion. In the context of a research study, this has the advantage of reducing possible bias that might arise from investigator-controlled manual infusions. Our computer-controlled system used a simple algorithm that is not dissimilar to manual-controlled algorithms.[36] Importantly, norepinephrine has the advantages of a fast onset of action and short duration which are desirable properties for a drug that is titrated by infusion. However, we acknowledge that some clinicians favor the use of intermittent boluses of vasopressors rather than infusions.[37] Further work is required to determine the efficacy of norepinephrine given by manually controlled infusion and intermittent boluses in obstetric patients.

In summary, our results showed that compared with phenylephrine, norepinephrine had similar efficacy for maintaining blood pressure during spinal anesthesia for cesarean delivery but with maintenance of greater maternal HR and CO. Neonatal outcome was similar. We suggest further work be done to determine the safety of norepinephrine in

obstetric patients, evaluate other methods of administration, determine its relative potency *versus* phenylephrine, and investigate whether its use may possibly be associated with greater uteroplacental blood flow and oxygen delivery compared with phenylephrine, particularly in conditions where uteroplacental perfusion is restricted such as preeclampsia.

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Competing Interests

The authors declare no competing interests.

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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. Epinephrine and norepinephrine were measured by using high-performance liquid chromatography with electrochemical detection. The catecholamines were isolated 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 an electrochemical detection system. The analytes were separated on a reversed-phased column (Ultrasphere IP C18; Beckman Instruments Inc., USA), 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 (Coulochem III; Thermo Scientific Dionex, USA). 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 0.9970. 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 3.71 to 13.11% (mean, 7.81%) and 2.67 to 9.79% (mean, 6.00 %), respectively. The between-day coefficients of variation were 6.46 to 15.06% (mean, 10.80%) and 7.84 to 13.68% (mean, 10.61%), respectively.