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Hemodynamic Effects of Ephedrine, Phenylephrine, and the Coadministration of Phenylephrine with Oxytocin during Spinal Anesthesia for Elective Cesarean Delivery

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Background: **Hemodynamic responses to vasopressors used during spinal anesthesia for elective Cesarean delivery, have not been well described. This study compared the effects of bolus phenylephrine and ephedrine on maternal cardiac output (CO). The hypothesis was that phenylephrine, but not ephedrine, decreases CO when administered in response to hypotension during spinal anesthesia.**

Methods: **Forty-three patients were randomized to receive 80 μg of phenylephrine or 10 mg of ephedrine. Both pulse wave form analysis and transthoracic bioimpedance changes were used to estimate stroke volume in each patient. Hemodynamic responses to spinal anesthesia and oxytocin were also recorded. A subgroup of 20 patients was randomized to receive oxytocin compared with oxytocin plus 80 μg of phenylephrine after delivery.**

Results: **Mean CO and maximum absolute response in CO were significantly lower during the 150 s after phenylephrine administration than after ephedrine (6.2 *vs.* 8.1 l/min, $P = 0.001$, and 5.2 *vs.* 9.0 l/min, $P < 0.0001$, respectively for pulse wave form analysis, and 5.2 *vs.* 6.3 l/min, $P = 0.01$ and 4.5 *vs.* 6.7 l/min, $P = 0.0001$, respectively for bioimpedance changes). CO changes correlated with heart rate changes. Coadministration of phenylephrine obtunded oxytocin-induced decreases in systemic vascular resistance and increases in heart rate and CO. Trends in CO change were similar using either monitor.**

Conclusions: **Bolus phenylephrine reduced maternal CO, and decreased CO when compared with ephedrine during elective spinal anesthesia for Cesarean delivery. CO changes correlated with heart rate changes after vasopressor administration, emphasizing the importance of heart rate as a surrogate indicator of CO. Coadministered phenylephrine obtunded hemodynamic responses to oxytocin.**

SPINAL anesthesia (SA) for Cesarean delivery (CD) may be associated with significant hemodynamic changes. Anesthesiologists conventionally use heart rate (HR) and noninvasive blood pressure recordings, as well as patient symptoms, to assess patient wellbeing. Vasopressors are used to restore blood pressure to baseline values. However, both from the maternal and fetal point of view, the preservation of cardiac output (CO) may be as important. A complete understanding of the hemodynamic responses to SA and to the administration of vasopressors would thus be of importance in the appropriate choice of vasopressor and dose in this clinical situation.

The effects of the two commonly used vasopressors, ephedrine and phenylephrine, on neonatal acid base status, a surrogate marker for neonatal wellbeing, have been extensively studied during SA for CD. Recent work shows that ephedrine is associated with a greater degree of neonatal acidosis than phenylephrine, probably on the basis that ephedrine crosses the placenta and causes a β-adrenergically mediated increase in fetal metabolic rate. This, together with a lower incidence of maternal symptoms, has led to a change in practice and a resurgence of the use of phenylephrine for spinal hypotension.[1] There have been very few investigations comparing the effects of the two vasopressors on maternal cardiovascular indices other than HR and blood pressure during SA for CD. Only one previously published study, employing intermittent suprasternal Doppler flow measurements, has compared CO changes using the two vasopressors during SA for CD. In this study, which compared bolus doses of the vasopressors, bradycardia in the phenylephrine group was treated with atropine, which makes the results difficult to interpret.[2] The primary outcome variable in this study was umbilical artery pH, and not maternal hemodynamic changes. There have been no investigations using beat-by-beat CO measurements. There is currently a condition of equipoise with regards to the use of the two vasopressors, as far as the restoration of maternal blood pressure is concerned. Our hypothesis, based on the limited literature and a study on patients with severe preeclampsia during SA for CD in our institution,[3] is that phenylephrine, but not ephedrine, decreases CO when administered in response to hypotension during SA for CD. Thus phenylephrine might be the better agent to restore systemic vascular resistance (SVR) to normal when hypotension is associated with vasodilation and a partial compensatory increase in CO in response to SA.[4] Ephedrine may be a better choice should severe hypotension and bradycardia occur, reflecting decreased CO. The primary outcome of our prospective randomized, double-blind study was thus a comparison of the time-based effects on maternal CO of bolus administration of the vasopressors phenylephrine and ephedrine during SA for CD. The

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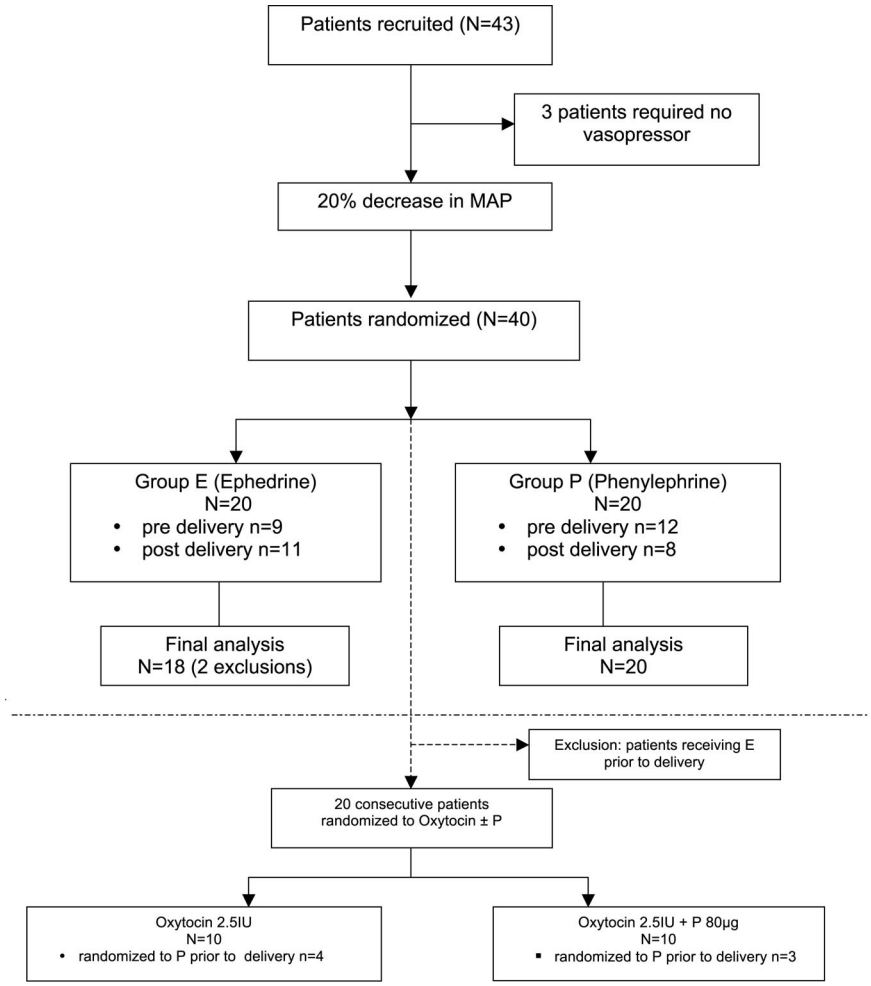

Fig. 1. Flow diagram of the trial protocol. MAP = mean arterial pressure.

LiDCO*plus* monitor (LiDCO, Cambridge, United Kingdom), which employs pulse wave form analysis calibrated with lithium dilution, was employed for the study. In addition, a monitor of transthoracic bioimpedance changes was also used in each patient to corroborate the results.

Secondary outcomes were the effects of SA on maternal hemodynamics, a comparison of the effects of oxytocin on maternal CO as measured by the two monitors and the effects of the coadministration of phenylephrine with oxytocin in obtunding the unwanted hemodynamic effects of oxytocin. Also recorded were neonatal Apgar scores, umbilical arterial and venous pH, and base deficit.

Materials and Methods

The study was prospective, randomized, and double-blind. Forty healthy patients scheduled for elective CD under SA were randomized to receive either phenylephrine (Group P) or ephedrine (Group E) as the initial vasopressor for the management of hypotension during SA. Randomization was performed at the time at which a vasopressor was first required. Blocked randomization was used (randomized block sizes of 4, 6, or 8, using nQuery Advisor Version 6, Statistical Solutions, Cork, Ireland), and sealed envelopes were prepared by the statistician. The trigger for vasopressor administration was defined as a 20% decrease from baseline mean arterial pressure at any time during the 45-min postinduction of SA other than during the delivery and for the 3 min thereafter. In addition, a subgroup of 20 consecutive patients who had not received prior ephedrine were randomized to receive either oxytocin alone or oxytocin mixed with phenylephrine IV after delivery. The flow diagram of the protocol is shown in figure 1.

Exclusions were anemia (hemoglobin < 9 g/dl), expected blood loss more than 700 ml, body mass index greater than 35 kg/m^2, multiple gestation, preeclampsia, cardiac, respiratory or renal disease, known allergy to any protocol medication, or age below 18 yr or above 40 yr. Written informed consent was obtained after approval from the University of Cape Town Ethics Committee (Cape Town, Western Cape, South Africa). Technical failure or inadequate anesthesia requiring conversion to general anesthesia would result in inclusion in the analysis of only the

data collected before the time of the decision to proceed with general anesthesia.

A detailed consent form was supplied to the patient the day before CD, and the procedure was explained to the patient either by the recruiting investigator or by a skilled translator. Consent was signed a minimum of 12 h after the information sheet had been discussed with the patient. Height (cm) and weight (kg) were measured, and body mass index was calculated.

Sodium citrate (30 ml) was given orally immediately preoperatively. Before SA, intravenous access was established by using a 16-gauge cannula under local anesthesia, and 1 g of cefazolin was slowly administered intravenously. Standard noninvasive monitoring consisted of electrocardiography and pulse oximetry. CO measurements were derived from two independent monitors in each patient. Transthoracic bioimpedance changes were monitored by using the BioZ instrument (Cardio Dynamics International, San Diego, CA). For this purpose, four pairs of bioimpedance electrodes were placed: two pairs opposite each other in the lower anterior cervical region and two pairs in the eighth to eleventh thoracic interspace in the midaxillary line. A 20-gauge radial arterial catheter was then placed under local anesthesia. The LiDCO*plus* monitor was then calibrated by using lithium dilution, employing at least two but not more than three separate determinations 5 min apart. The average calibration factor was calculated and entered. Data from each consecutive pulse wave form was recorded on an Excel chart (Microsoft, Redmond, WA) from 5 min before SA until the end of surgery or until 45 min after induction of anesthesia if the duration of surgery was less than 45 min. Recorded data consisted of HR, systolic, diastolic, and mean arterial pressure (MAP), and CO. Central venous pressure was given an arbitrary value of 5 mmHg for the purposes of calculation of SVR. CO measurements derived from bioimpedance changes during left ventricular ejection, were averaged every 10 beats and recorded every 5 s on an Excel chart. Beat by beat stroke volume (SV) estimates and CO were derived from the LiDCOplus monitor by using the proprietary algorithm. The time-base for the two monitors was synchronized.

Baseline pulse waveform- and bioimpedance-derived data were recorded and averaged during a continuous 2-min period before sitting up for SA, with the patient in the left lateral position. During this period, baseline MAP was also recorded. Baseline MAP was taken as the mean of three consecutive readings at least 45 s apart, not differing from one another by more than 10%. The target MAP (80% of baseline) for vasopressor administration was calculated from this baseline value.

The management of SA was as follows. Modified Ringer's lactate solution (20 ml/kg) was administered as a rapid crystalloid coload, initiated after cerebrospinal fluid appeared in the hub of the spinal needle. Less than 100 ml of crystalloid solution was administered thereafter, unless blood loss, estimated from suction bottle measurement and inspection of swabs, was excessive; in which case, the patient would be excluded from treatment *via* the trial protocol and would be treated per the usual protocol for blood loss. All patients received 2.0 ml of hyperbaric 0.5% bupivacaine (10 mg) plus 10 μg of fentanyl administered over 20 s at the L3/4 interspace. After 20 s in the sitting position, patients were positioned supine, with at least 15 degrees of left lateral tilt, to minimize aortocaval compression. Block height was assessed by using cold sensitivity to ethyl chloride spray. No supplemental oxygen was administered unless oxygen saturation decreased to less than 92%.

The anesthesiologist, blinded to the LiDCO*plus* and BioZ measurements, responded to HR and MAP changes as is normal clinical practice during SA for CD. One 5-ml syringe containing the randomly assigned vasopressor, and another containing the alternative vasopressor (*i.e.*, either 80 μg/ml phenylephrine or 10 mg/ml ephedrine in water) were prepared by an anesthesiologist not involved with the intraoperative management. If MAP decreased by 20% from the baseline value, 1 ml of the randomly assigned vasopressor was administered every 60 s until MAP recovered to within 20% of baseline. Randomization would thus only be done at the point when a vasopressor intervention was indicated.

Should MAP continue to decrease to 40% below baseline after 45 s, a rescue dose of the same vasopressor would be given. Should MAP not be restored to within 20% of baseline after two successive doses of vasopressor within 2 min, the alternative vasopressor would be used, according to the same protocol. The anesthesiologist performing SA was blinded to the vasopressor used. Should HR decrease to less than 55 beats/min in association with severe hypotension (30% below baseline), atropine 0.5 mg and ephedrine 10 mg would be administered. In the event of severe hypotension unresponsive to atropine and ephedrine, adrenaline would be administered in titrated boluses. After a total of 5 doses of the same vasopressor, if MAP again decreased by more than 20% of baseline, the alternative vasopressor was used. No patient was to be given more than 5 doses of ephedrine (50 mg) because this would be interpreted as tachyphylaxis.

Thirty seconds after delivery, 2.5 IU of oxytocin in 10 ml of water was administered intravenously over a period of 30 s to all patients receiving ephedrine before delivery and to all other patients except for a subgroup of 20 consecutive patients not having received ephedrine before delivery. These 20 patients were randomized to receive intravenously either 2.5 IU of oxytocin or 2.5 IU of oxytocin mixed with 80 μg of phenylephrine in 10 ml of water over a period of 30 s starting 30 s after delivery. For this purpose, a preprepared sealed envelope was opened immediately before delivery. The an-

esthesiologist administering oxytocin was blinded as to the treatment group. No further vasopressor was administered for up to 3 min after oxytocin administration. The obstetrician was asked to grade uterine contraction as good, adequate, or inadequate and requiring further oxytocin, and this was recorded.

Intraoperative blood loss was estimated from suction bottle measurements and inspection of swabs. Neonatal Apgar scores, umbilical arterial and venous pH and base deficit, and neonatal weight were recorded.

Statistical Analysis

The primary outcome variable was the change in CO in response to the initial dose of vasopressor. A recent study in our institution using the LiDCO*plus* monitor involving the use of ephedrine and phenylephrine during SA for CD in severe preeclampsia, suggested that a between-group difference in mean CO change would approximate 0.4 l/min.[3] A sample size of 17 in each group would have 80% power to detect a difference in means of 0.4 l/min, assuming that the common SD was 0.4 l using a two-group *t* test with a 0.05 two-sided significance level. It was expected that only 70% of the women undergoing elective CD would require a vasopressor; therefore, the study would aim to recruit a minimum of 50 women.

Prevasopressor values were taken as the mean value for the period 30 s before vasopressor administration. Peak effect was taken as the mean value for the 5 s before and after the time of maximum change in CO value recorded in the 150 s after vasopressor administration. The mean absolute CO was calculated as the average CO over 150 s after vasopressor administration. The peak and mean percentage change from prevasopressor values for each vasopressor were calculated. CO changes were related to both the prevasopressor value and the baseline value. The area under the curve for this period was also calculated and compared between vasopressors. The correlation between percentage change in peak CO and HR was compared using a linear regression model. The slopes of the group-specific regression lines of CO on HR were compared.

Secondary outcomes were the response to SA and the response to oxytocin. The hemodynamic response to SA was estimated by comparing the hemodynamic measurements at baseline with those at the prevasopressor time interval in patients receiving vasopressor predelivery or with averaged values for the 30-s period immediately before uterine incision if no predelivery vasopressor was required.

The response to oxytocin was analyzed as follows: hemodynamic data were averaged for 30 s before the administration of oxytocin. As for the vasopressors, the subsequent data were plotted against time to ascertain the time to maximum effect of oxytocin (taken as the highest value of CO), and the maximum response to oxytocin was estimated by averaging the data for 5 s before and after this point. In the 20 patients randomized to receive either oxytocin or the oxytocin-phenylephrine mixture, the change in hemodynamic variables was compared. A sample size of five patients in each group would have 90% power to detect a difference in mean CO of 25% assuming that the common SD is 10%, using a two group *t* test with a 0.05 two-sided significance level. Therefore, 10 patients were included in each group.

The two-sample *t* test was used for comparison of all the hemodynamic parameters. The estimated mean difference and the 95% confidence intervals were reported. To account for the multiple testing performed, the false discovery rate was controlled by applying the method of Benjamini and Hochberg.[5] The required *P* value limit was calculated for the main study and the substudy, and these bounds are indicated in the legends of the tables reporting the inference results.

To depict the summary profile of the response to vasopressor or oxytocin administration in the two groups, a median smooth was used. This approach gave an estimate that was robust to extreme values and sensitive to acute changes in hemodynamic variables. These were presented as graphic ensembles.

The influence of the administration of vasopressor before or after delivery was formally evaluated by a regression analysis which included the vasopressor, timing, and interaction effects for the mean and percentage peak values of the hemodynamic parameters CO and HR during the 150 s after vasopressor administration.

By using the method described by Bland and Altman[6] for assessing agreement between measurement techniques, the bias (mean difference) and limits of agreement (bias $\pm$ 2 SD) between CO measured by LiDCO*plus* and transthoracic bioimpedance technology were determined and used to summarize the level of agreement between the methods. CO was compared under baseline conditions, immediately before uterine incision, and after delivery. The first time interval was taken as averaged CO data for the 2-min period during baseline measurements, until 30 s before the patient sat up for SA. The second period was taken as averaged data for the 30 s before uterine incision, and the third used averaged data for 1 min, starting at 40 min after performance of SA. The analysis was based on all the women recruited into the study.

All statistical analyses were performed using SAS version 12 (SAS Institute Inc., Cary, NC).

Results

Forty-three patients were recruited to this prospective randomized study, between November 20, 2007 and

Table 1. Details of Vasopressor Use

	Group E (n = 20)			Group P (n = 20)		
	n	Dose (mg)	Range	n	Dose (μg)	Range
Ephedrine pre, mg	9	22.2	10–40	0	0	—
Ephedrine post, mg	18	21.7	10–50	13	24.6	10–50
Phenylephrine pre, μg	0	0	—	12	166.7	80–240
Phenylephrine post, μg	6	293.3	80–640	20	266	80–800

Group E = ephedrine; Group P = phenylephrine as the vasopressor of first use; pre = vasopressor administered predelivery; post = vasopressor administered postdelivery. Most patients receiving vasopressor before delivery also received vasopressor postdelivery.

March 11, 2008. The initial power analysis assumed that 70% of patients would require a vasopressor. Thus 50 patients would have been required to randomize 34 patients to vasopressor treatment. In fact, only 3 patients of the first 43 did not require vasopressor, so that the study could be concluded at this point, with 20 patients in each treatment group at this time. The primary outcome data of two patients in Group E could not be used. One computer file was corrupted, and in the other, persistent vomiting before vasopressor administration necessitated the omission of the data. Thus the final analysis of the primary outcome data compared 20 patients in Group P with 18 patients in Group E. No patients received both vasopressors predelivery. In the final analysis, 9 of 18 patients in Group E and 12 of 20 patients in Group P received the first dose of vasopressor predelivery (fig. 1). In Group P, 13 patients required ephedrine after delivery; in Group E, 6 patients required phenylephrine postdelivery as per protocol. Vasopressor use is summarized in table 1.

Demographic and relevant data pertaining to anesthesia, surgery, and neonatal outcome appear in table 2. Considering patients receiving vasopressor predelivery, there were significant between-group differences in standard bicarbonate, umbilical arterial base excess, and umbilical arterial Po_2. There were no other between-group differences, and no patients required analgesic supplementation. The occurrence of nausea and vomiting was recorded after the first vasopressor administered. This occurred in four patients who received ephedrine as the initial vasopressor, and two patients who receive phenylephrine (ns).

The primary outcome of this study was a comparison of the change in CO after the first administration of ephedrine or phenylephrine in response to hypotension. Tables 3 and 4 show hemodynamic data at baseline, at the time of randomization to the vasopressor (*i.e.*, at target mean arterial blood pressure or 80% of baseline) and after vasopressor administration. There were no significant between-group differences in any measure

Table 2. Demographic and Relevant Data Pertaining to Anesthesia, Surgery, and Neonatal Outcome

	Group E		Group P		
	Mean/Median	SD/Range	Mean/Median	SD/Range	*P* Value
Height, cm	158.4	6.5	156.6	5.7	NS
Weight, kg	76.9	11.8	73.7	11.8	NS
Age, yr	26.4	4.1	27.1	3.7	NS
Gravidity, n	2	1–4	2	1–4	NS
Parity, n	1	0–2	1	0–2	NS
Uterine incision, s	917	185	940	226	NS
Delivery, s	73	28	86	33	NS
Coload Volume, ml	1,537	234	1,480	264	NS
Coload Time, s	1,274	435	1,259	416	NS
Block Height	T3	T2–T5	T3	T2–T5	NS
Blood loss, ml	398	44	378	30	NS
Apgar 1 min	9	7–10	9	6–9	NS
Apgar 5 min	9	9–10	9.5	9–10	NS
UA pH*	7.28	0.06	7.31	0.04	NS
UA PCO_2*, kPa	6.48	1.82	6.98	1.12	NS
UA PO_2*, kPa	2.02	0.51	1.59	0.39	0.049
UA SBC*, mmol/l	18.83	2.25	21.28	2.45	0.036
UA Base excess*, mmol/l	–4.75	3.04	–1.34	3.06	0.025

* Data pertains to patients who received vasopressor predelivery (n = 9 in Group E, n = 12 in Group P).

Delivery = time from uterine incision to delivery; Group E = ephedrine; Group P = phenylephrine as the vasopressor of first use; PCO_2 = partial pressure of carbon dioxide; PO_2 = partial pressure of oxygen; SBC = standard bicarbonate; UA = umbilical arterial; uterine incision = time from induction of spinal anesthesia to uterine incision.

Table 3. Baseline and Prevasopressor Hemodynamics

	Group E (n = 18)		Group P (n = 20)			95% CI		
	Mean	SD	Mean	SD	Difference	Lower Limit	Upper Limit	*P* Value
Baseline								
HR, beats/min	83.6	9.8	80.4	10.7	3.2	–3.5	9.9	0.3375
MAP, mmHg	90.5	10.3	91.5	10.9	–1.0	–7.9	5.9	0.7776
SV, ml/beat	73.7	15.2	73.5	18.2	0.2	–10.7	11.1	0.9747
SVR, Dyne · s · cm^{-5}	1177.5	315.6	1241.2	266.9	–63.7	–253.0	125.6	0.4994
CO(LiDCO), l/min	6.2	1.6	5.8	1.2	0.4	–0.6	1.3	0.4322
CO(BioZ), l/min	5.3	0.8	4.6	0.9	0.7	0.1	1.2	0.0202
Prevasopressor								
HR, beats/min	91.7	12.7	91.5	17.6	0.1	–10.1	10.3	0.9772
MAP, mmHg	71.8	7.1	72.8	7.1	–1.0	–5.7	3.7	0.6560
SV, ml/beat	85.7	21.0	80.2	16.1	5.5	–6.8	17.7	0.3705
SVR, Dyne · s · cm^{-5}	746.1	272.4	782.6	169.3	–36.5	–184.1	111.1	0.6190
CO(LiDCO), l/min	7.9	2.4	7.2	1.4	0.7	–0.6	2.0	0.3058
CO(BioZ), l/min	6.1	1.1	5.7	1.6	0.5	–0.4	1.4	0.3024

CI = confidence interval; CO(LiDCO) and CO(BioZ) = cardiac output derived using the LiDCO*plus* (LiDCO, Cambridge, United Kingdom) and BioZ (Cardio Dynamics International, San Diego, CA) monitors respectively; HR = heart rate; MAP = mean arterial pressure; prevasopressor = hemodynamic values prior to the first administration of either vasopressor (at time of randomisation); SV = stroke volume; SVR = systemic vascular resistance.

either at baseline or before vasopressor administration, except for a small baseline difference in the CO as measured by the BioZ system. Detailed data shown pertaining to the response to vasopressor administration are the mean absolute values, as well as peak and percentage change in HR, SV, CO, MAP, and SVR, the times after vasopressor administration to the peak values, and the area under the curve for MAP and CO changes, during the 150 s after the first administration of vasopressor in the two groups. The CO changes are shown as measured by both the LiDCO*plus* and BioZ monitors. After vasopressor administration, between-group differences in HR were significant both in absolute terms and in the percentage change at peak effect. Phenylephrine was associated with a reduction in HR. Mean arterial pressure increased in both groups with a greater increase in absolute and peak pressure as well as in the sustained response as measured by the area under the curve in Group P. The time to peak MAP was significantly shorter with phenylephrine than with ephedrine. In both groups, the objective was achieved of restoring MAP to within 20% of baseline. The mean peak postvasopressor MAP was 8% below the baseline value in Group E and 8% above baseline in Group P. SV was not significantly different between the two groups. Mean CO and maximum absolute response in CO were significantly lower in the 150 s after phenylephrine administration than after ephedrine: 6.2 *versus* 8.1 l/min, ($P = 0.001$) and 5.2 *versus* 9.0 l/min ($P < 0.0001$), respectively for pulse wave form analysis. The corresponding values for bioimpedance changes were 5.2 *versus* 6.3 l/min ($P = 0.01$) and 4.5 *versus* 6.7 l/min, ($P = 0.0001$), respectively.

Figure 2 shows median HR, CO, MAP, and SVR and SV changes, respectively, estimated by the LiDCO*plus* monitor in the 150 s after vasopressor. Note that the maximum rate of change in HR was early after phenylephrine administration, although the time to peak change was longer and similar to that for ephedrine (table 4). The time to peak change in CO was significantly different between groups. There was a similar positive correlation between CO and HR changes in each group ($P = 0.87$ for the comparison between the regression lines) (fig. 3).

Figure 4 shows a comparison of time-based changes in CO recorded by the LiDCO*plus* and BioZ monitor in the 150 s after vasopressor. Individual responses are shown as thin gray lines, and the ensemble median value is depicted as a superimposed thick black line. Both CO monitors showed a significant between-group difference in the percentage CO change and in the same direction after the first vasopressor administration. The difference between the instruments with respect to the percentage change in CO was significantly different between the two vasopressor groups. Group P had larger differences between the instruments than Group E (fig. 5) and a weaker correlation between the measurements (r = 0.08 and 0.56, respectively).

Figure 6 shows a between-group comparison of percentage change from prevasopressor values of CO and HR in patients receiving vasopressor either before or after delivery. The mean and percentage peak between-group differences in CO and HR for the 150 s after vasopressor administration were not significantly different before and after delivery ($P = 0.55$ and 0.67 for mean and 0.75 and 0.09 for percentage peak change in CO and HR, respectively).

The secondary outcome of the effects of SA on hemodynamics during the predelivery period is shown in figure 7. This is presented as a percentage change from baseline at the prevasopressor time interval in patients receiving vasopressor before delivery or at the preuterine incision time interval for those patients not receiving vasopressor predelivery. At the prevasopressor time in-

Table 4. Hemodynamic Response to Vasopressor Administration

	Group E (n=18)		Group P (n=20)			95% CI		
	Mean	SD	Mean	SD	Difference	Lower Limit	Upper Limit	P Value*
Postvasopressor								
HR								
Absolute, beats/min	92.4	12.4	76.9	12.7	15.5	7.2	23.8	0.0005
AUC	59.9	812.7	–2325.0	1638.0	2384.8	1518.6	3250.9	<.0001
Peak, beats/min	97.2	13.3	67.4	11.7	29.8	21.6	38.0	<.0001
Percent-peak, %	7.0	14.8	–25.5	9.8	32.5	24.3	40.7	<.0001
Time to peak, s	66.3	37.2	62.6	35.3	3.7	37.2	35.3	0.7547
MAP								
Absolute, beats/min	78.2	8.6	86.3	9.1	–8.1	–13.9	–2.3	0.0078
AUC	1020.3	853.6	2104.2	1071.6	–1084.0	–1726.0	–441.7	0.0016
Peak, beats/min	83.3	11.6	98.5	9.6	–15.2	–22.2	–8.2	<.0001
Percent-peak, %	16.5	14.8	35.7	11.2	–19.2	–27.8	–19.2	<.0001
Time to peak, s	89.8	38.5	61.8	35.2	28.0	3.8	52.3	0.0247
SV								
Absolute, ml/beat	87.9	20.0	81.4	17.2	6.5	–5.7	18.7	0.2876
Peak, ml/beat	89.4	20.0	80.2	20.8	9.2	–4.3	22.7	0.3705
Percent-peak, %	5.7	12.6	0.1	17.7	5.6	–4.6	15.9	0.2737
Time to peak, s	83.2	40.2	76.4	48.7	6.8	–22.8	36.4	0.6441
SVR								
Absolute, Dyne · s · cm^{-5}	782.8	265.4	1123.7	259.7	–340.9	–513.8	–168.0	0.0003
Peak, Dyne · s · cm^{-5}	822.6	315.7	1450.5	370.0	–627.9	–855.5	–400.3	<.0001
Percent-peak, %	14.7	37.1	86.0	30.7	–71.3	–93.7	–49.0	<.0001
Time to peak, s	83.6	46.5	35.4	17.2	48.3	25.7	70.9	0.0004
CO(LiDCO)								
Absolute, l/min	8.1	2.0	6.2	1.3	1.9	0.8	3.1	0.0011
AUC	26.9	150.4	–160.6	122.7	187.4	97.5	277.4	0.0002
Peak, l/min	9.0	2.7	5.2	1.4	3.8	2.1	4.0	<.0001
Percent-peak, %	16.0	19.5	–27.8	10.7	43.8	33.6	54.0	<.0001
Time to peak, s	58.8	36.2	32.2	11.1	26.6	9.4	43.9	0.0072
CO(BioZ)								
Absolute, l/min	6.3	1.1	5.2	1.5	1.1	0.3	2.0	0.0111
AUC	15.9	51.1	–77.1	57.5	93.0	57.1	129.0	<.0001
Peak, l/min	6.7	1.6	4.5	1.5	2.2	1.2	3.2	0.0001
Percent-peak, %	8.5	19.3	–21.8	7.3	30.2	20.3	40.1	<.0001
Time to peak, s	92.7	42.2	68.7	28.8	24.0	0.5	47.6	0.0459

* = false discovery rate bound is 0.0247.

Absolute = the averaged change in the absolute value from prevasopressor value over 150 s after vasopressor administration; AUC = area under curve for change in variable from prevasopressor value for 150 s after vasopressor administration; CI = confidence interval; CO(LiDCO) and CO(BioZ) = cardiac output derived using the LiDCO*plus* (LiDCO, Cambridge, United Kingdom) and BioZ (Cardio Dynamics International, San Diego, CA) monitors respectively; HR = heart rate; MAP = mean arterial pressure; Peak = maximum absolute response of each variable to vasopressor; Percent-peak = percentage change in variable from prevasopressor value at peak value; Post-vasopressor = hemodynamic values after the first administration of either vasopressor; SV = stroke volume; SVR = systemic vascular resistance.

terval, CO had increased significantly from baseline values, due to an increase in HR and SV. In patients not requiring vasopressor before the preuterine incision time interval, CO had also increased significantly as a result of an increase in SV alone.

Figure 8A shows median smooth plots of the responses (percentage change in HR, MAP, SV, and SVR from preoxytocin values) of the 20 patients randomized to receive either oxytocin 2.5 IU alone, or a mixture of oxytocin 2.5 IU and phenylephrine 80 μg. Ensembles of time-based changes in CO recorded by the LiDCO*plus* and BioZ monitors are also shown (fig. 8B). Table 5 shows a detailed between-group comparison of hemodynamic parameters before and after administration of oxytocin or the oxytocin/phenylephrine mixture. Absolute peak HR and CO were lower, and SVR and MAP significantly higher in the group receiving the mixture. Percentage changes in these parameters were also significantly different in the two groups. Times to peak changes were also different, with the exception of SV and CO changes. The BioZ monitor showed a similar trend in CO change, but between-group differences were not significant. In all patients, uterine contraction was assessed by the obstetrician as good. Figure 9 shows ensembles of responses to oxytocin (percentage change in CO and SVR from the preoxytocin values) in the 32 patients receiving oxytocin alone, derived from the LiDCO*plus* monitor, and comparative CO data from the BioZ monitor.

Bland and Altman comparison of pulse wave form analysis (LiDCO*plus*) and bioimpedance changes (BioZ) was performed at three measurement periods (baseline, preuterine incision, and 40 min after induction of SA).

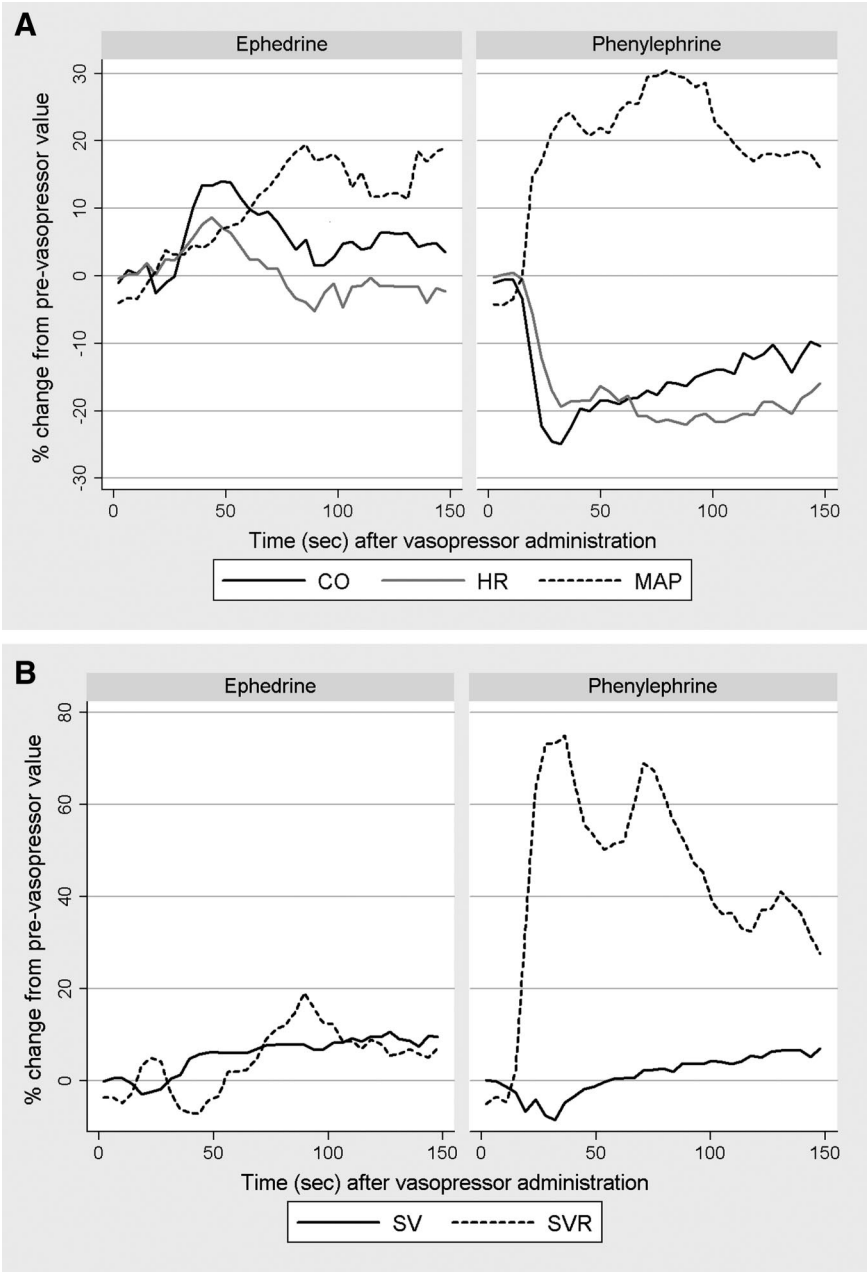

Fig. 2. (*A*) Percentage changes from prevasopressor values in cardiac output (CO, as measured by LiDCO*plus* monitors; LiDCO, Cambridge, United Kingdom), heart rate (HR), and mean arterial pressure (MAP) after the administration of vasopressor. *Lines* represent the median smooth for each parameter. (*B*) Percentage changes from prevasopressor values, in stroke volume (SV, as measured by LiDCO*plus* monitors), and systemic vascular resistance (SVR) after the administration of vasopressor. *Lines* represent the median smooth for each parameter.

The bias at each measurement point was 1.0, 1.0, and 1.6 l/min, respectively. The limits of agreement at each measurement point were –1.8 to 3.7, –1.9 to 3.9, and –2.0 to 5.2 l/min, respectively.

Discussion

This prospective randomized comparison of the effects of phenylephrine and ephedrine on maternal hemodynamics during SA for CD showed that an 80-μg bolus of phenylephrine caused a significantly lower maternal CO when compared to a 10-mg bolus dose of ephedrine, during the 150 s after vasopressor administration. However, the mean postphenylephrine CO values remained above baseline (tables 3 and 4), since CO values immediately before vasopressor administration were higher than baseline. The two CO monitors used, based upon pulse wave form analysis and transthoracic bioimpedance changes, recorded similar trends in changes in CO after vasopressor administration. The maximum change in HR was also significantly different between groups. There was a strong correlation between HR and CO in both groups after vasopressor administration. The peak changes in CO and MAP after phenylephrine occurred significantly earlier than those after ephedrine. SVR changes after the vasopressors suggested a marked rise in afterload after phenylephrine. After ephedrine administration, there was a sequence of

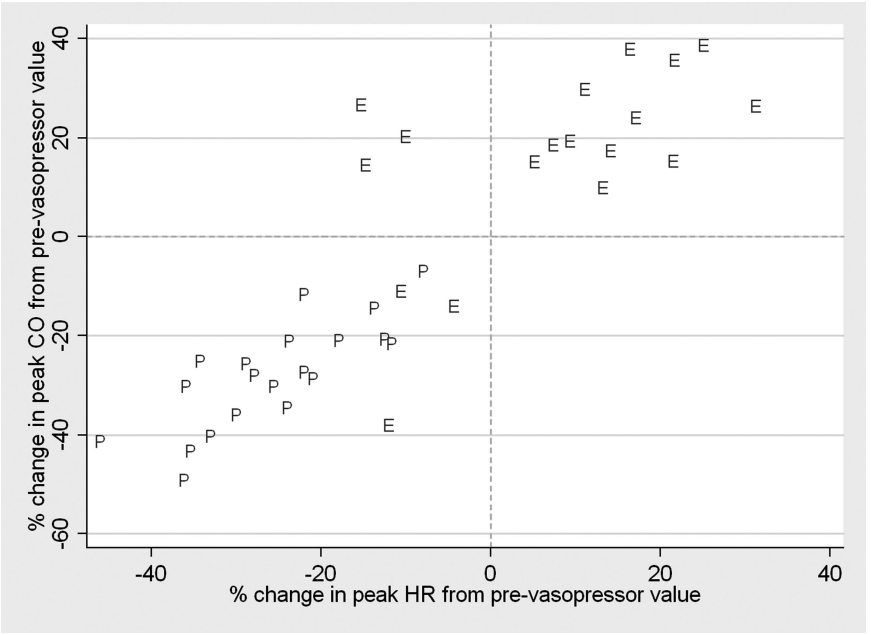

Fig. 3. Scatter plot showing the correlation between the percentage change in peak heart rate with percentage change in peak cardiac output from prevasopressor value, after vasopressor administration. For ephedrine: r = 0.65, *P* = 0.003; for phenylephrine: r = 0.87, *P* < 0.0001. CO = cardiac output; E = Ephedrine; HR = heart rate; P = Phenylephrine.

a transient increase in afterload, followed by a transient decrease (possibly β_2-mediated) and then a sustained increase in SVR (probably mediated by noradrenaline release) (fig. 2, A and B).

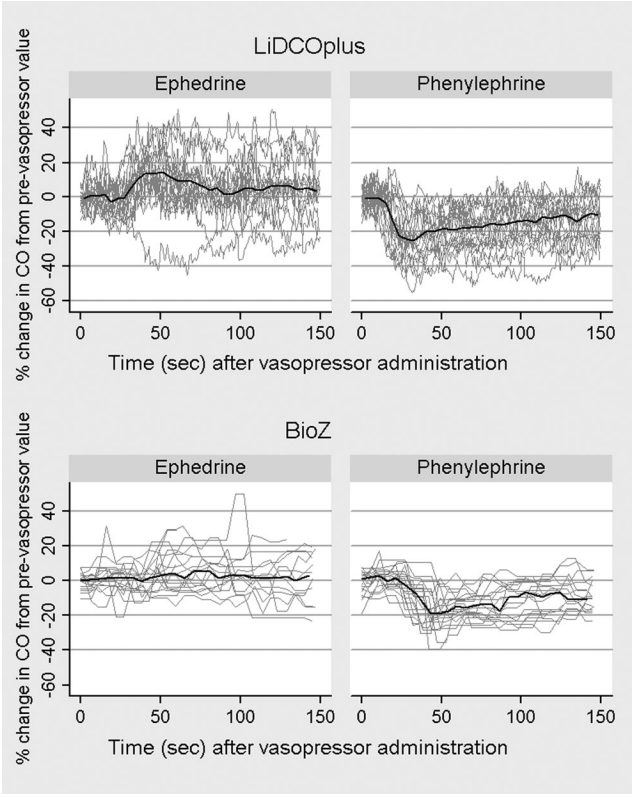

Fig. 4. Ensembles of percentage changes from prevasopressor values in cardiac output (CO) as measured with the LiDCO*plus* (LiDCO, Cambridge, United Kingdom) and the BioZ (Cardio Dynamics International, San Diego, CA) monitors. Each ensemble shows the percentage change for each patient (*light gray*) and the median smooth for the group (*black*) for the 150 s after administration of either ephedrine or phenylephrine.

Hemodynamic changes associated with SA for CD are of particular importance to anesthesiologists, both in terms of patient safety and comfort. Precipitous decreases in maternal CO, particularly when associated with bradycardia, may be life-threatening and place the fetus at risk of hypoxia and a poor neurologic outcome. Maternal hypotension is known to be associated with nausea and vomiting, which makes the experience of the delivery unpleasant for the mother. Fluid and vasopressor use should thus be appropriate for the specific hemodynamic disturbance encountered.

Previous studies have employed intermittent measurement of maternal CO, using indicator dilution or suprasternal Doppler flow technology.[2,7] In a randomized comparison of the effects of 5-mg bolus of ephedrine and 100-μg bolus of phenylephrine on maternal CO and cord gas values, overall CO changes were not different between groups.[2] These investigators used atropine in 11 of 19 cases of phenylephrine-associated bradycardia. This makes the interpretation of the mechanism of CO changes difficult. The study was primarily powered to

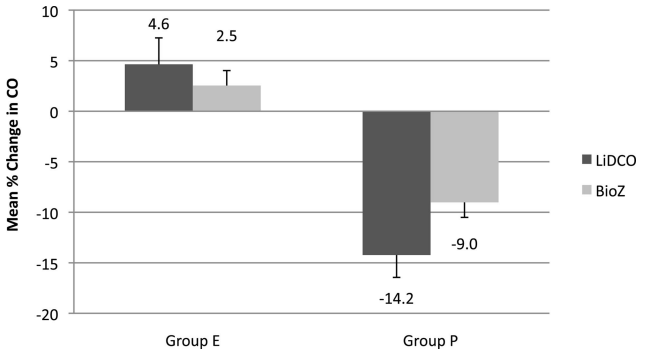

Fig. 5. Mean percentage changes in cardiac output (CO) for the 150 s after first vasopressor administration in each group as measured by each device. *Error bars* indicate SEM.

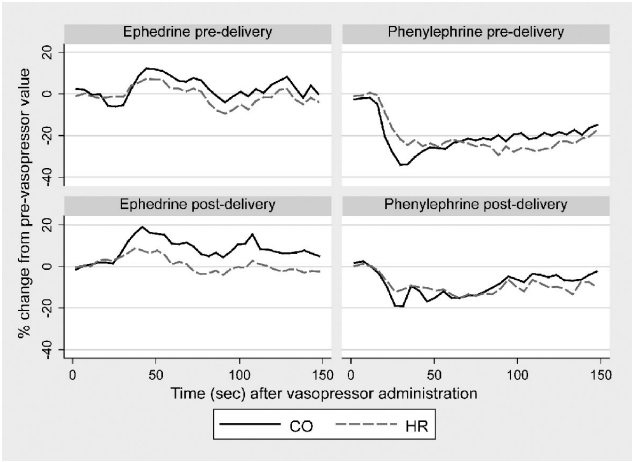

Fig. 6. Between-group comparison of patients receiving vasopressor before and after delivery. Percentage changes from prevasopressor values in CO (LiDCO*plus* monitors; LiDCO, Cambridge, United Kingdom) and HR after the administration of vasopressor. *Lines* represent the median smooth for each parameter. CO = cardiac output; HR = heart rate.

detect differences in umbilical artery pH, and it did not examine CO responses to individual boluses of vasopressor. In our trial, slowing of the HR after phenylephrine administration was not treated with anticholinergics if blood pressure was maintained or elevated after vasopressor administration.

There is considerable controversy as to the dose equivalence of phenylephrine and ephedrine for vasopressor effect. A recent investigation using continuous infusions found a potency ratio of 83:1.[8] Published studies have employed ratios varying from 20:1 to 250:1. Consensus was reached among the investigators that, in our patient population group, an 80-μg bolus of phenylephrine was equivalent to 10 mg of ephedrine, a 125:1 ratio. These were regarded as doses that would restore the MAP to within a range of 20% above or below baseline. The effectiveness of the dose may also be related to the time-to-peak effect. In the current study, phenylephrine had a peak pressor effect at 61.8 s, which was later than the peak depressant effect on CO (32.2 s). The peak pressor effect of ephedrine was at 89.8 s, and the peak change in CO was also earlier (58.8 s) than the peak pressor effect. In the case of phenylephrine, this could be the result of a gradual improvement in CO that was seen after the peak depressant effect (Anrep effect, see below). In the case of ephedrine, this could be explained by the early β_1 and β_2 effects, causing an increase in CO, followed by the indirect effect of release of norepinephrine from the sympathetic nerve terminals, resulting in the peak increase in blood pressure.

An early study of intermittent CO measurement during SA for CD, using indicator dilution, showed that maternal CO was significantly depressed in 10 of 12 patients and greatly improved by a change from the supine to the left lateral position.[7] A more recent investigation with intermittent suprasternal Doppler flow measurements, showed that SA using a median dose of 11 mg of bupivacaine was associated with a decrease in CO of more than 1 l/min in 9 of 16 patients.[9] A further study, using lower doses of local anesthetic (7 and 10 mg bupivacaine) in conjunction with subarachnoid sufentanil, demonstrated an increase in CO after SA, which was obtunded by the use of an infusion of phenylephrine at 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[4] In our trial using 10-mg spinal bupivacaine, careful left lateral tilt, and 20 ml/kg crystalloid coload, there was a significant decrease in SVR and an increase in HR, SV, and CO from the baseline value, at the time immediately before administration of vasopressor during the predelivery period, or in SV and CO at the time of uterine incision, if no vasopressor was required by this time (fig. 7). In an investigation of sympathovagal balance during SA in the nonobstetric population, the

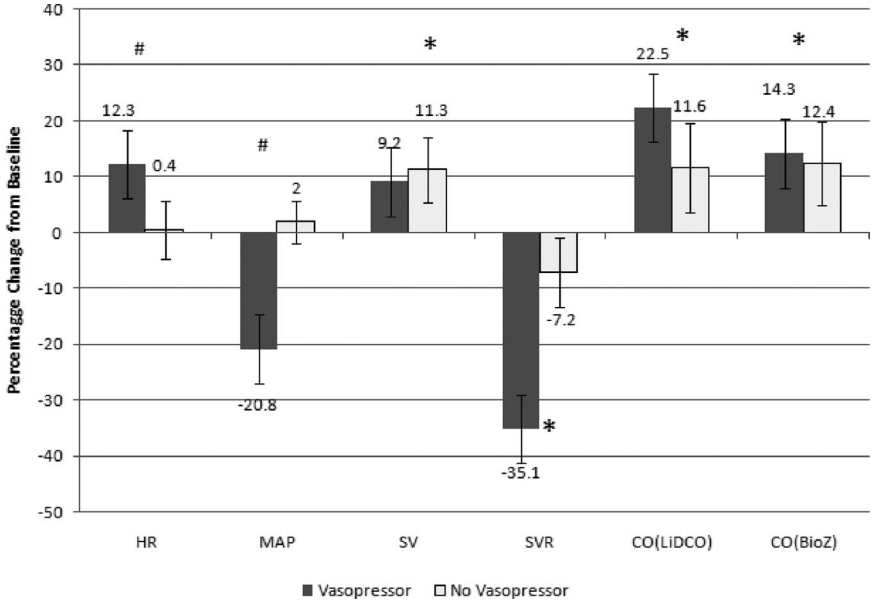

Fig. 7. Percentage hemodynamic changes from baseline at the prevasopressor time interval in those patients who received vasopressor before delivery (n = 20) or at the preuterine incision time interval for those patients not receiving vasopressor before delivery (n = 19). 95% confidence intervals indicated by the *error bars*. # $P < 0.05$ for changes from baseline in the subjects receiving vasopressor only; * $P < 0.05$ for changes from baseline for both vasopressor and no vasopressor subjects. CO (LiDCO*plus*) and CO (BioZ) = cardiac output derived using the LiDCO*plus* (Cambridge, United Kingdom) and BioZ (Cardio Dynamics International, San Diego, CA) monitors respectively; HR = heart rate; MAP = mean arterial pressure; SV = stroke volume; SVR = systemic vascular resistance.

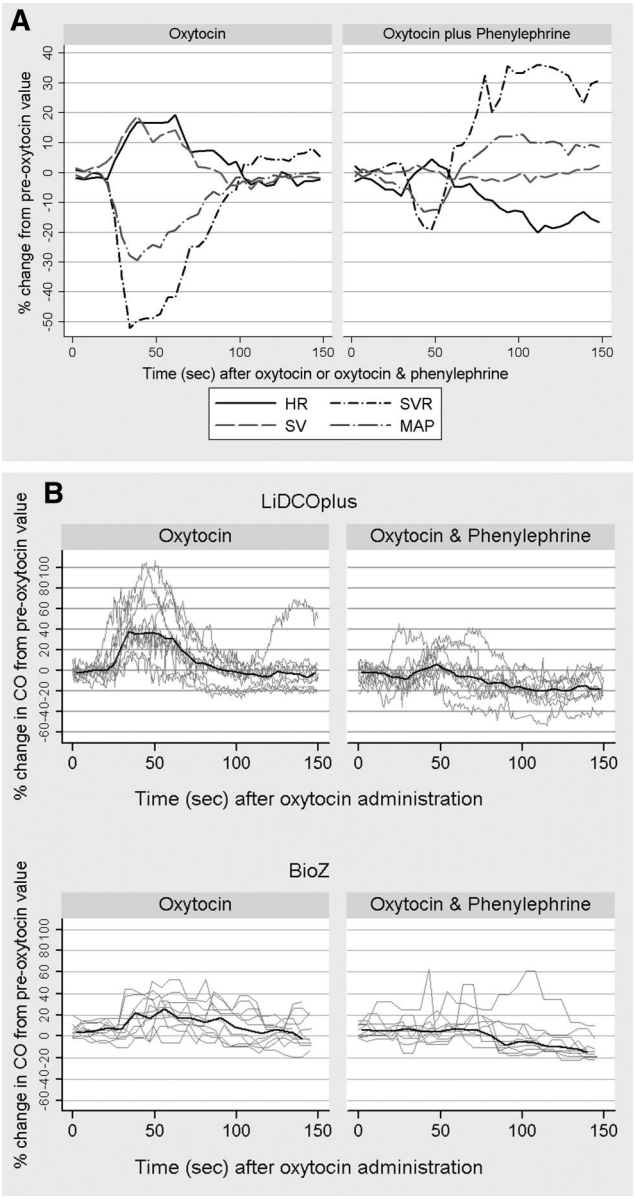

Fig. 8. (*A*) Median smooth plots of percentage changes from preoxytocin values in heart rate (HR), mean arterial pressure (MAP), stroke volume (SV), and systemic vascular resistance (SVR), for 20 patients receiving either oxytocin or oxytocin plus phenylephrine. (*B*) Ensembles of cardiac output (CO) changes from preoxytocin values as measured with the LiDCO*plus* (LiDCO, Cambridge, United Kingdom) and the BioZ (Cardio Dynamics International, San Diego, CA) monitors. Each ensemble shows the percentage change for each patient (*light gray*) and the median smooth for the group (black) for the 150 s after administration of either oxytocin or a mixture of oxytocin and phenylephrine.

maintenance of HR despite sympathetic denervation, has been attributed to concomitant diminished parasympathetic activity to the heart.[10] In our study, none of the 43 patients developed precipitous bradycardia in response to SA, and this event, possibly due to reflex activation of the vagus nerve as a result of failure of ventricular filling,[11] appears relatively uncommon. A recent editorial examining the relative contributions of the venous and arterial circulation to the hypotensive effects of SA, placed equal emphasis on arterial dilation as on decreased venous return.[12] In keeping with this view, a *post hoc* between-group comparison in the current study of the effects of vasopressor administered before or after delivery suggested that the differences in percentage changes in hemodynamic variables after ephedrine and phenylephrine were independent of the time of administration (fig. 6).

From these investigations, it therefore appears that modest hypotension during SA for CD (0–20% decrease in baseline blood pressure) is associated with a decrease in SVR, and in many cases, a partial compensatory increase in CO mediated by increases in HR and SV. The decrease in SVR may be effectively obtunded by the use of either low-dose boluses or a low-dose infusion of phenylephrine. Using suprasternal Doppler flow measurements during SA for CD, a dose-dependent reduction in CO has been demonstrated in parturients receiving an infusion of phenylephrine at 100 μg/min.[13] Thus, these studies and the current investigation suggest that doses of phenylephrine large enough to cause marked increases in MAP above baseline, and sinus bradycardia, would be associated with depression of CO to below baseline values and should be avoided. The strong correlation between HR and CO changes after both ephedrine and phenylephrine administration suggests that HR, and not MAP, is the most important surrogate marker of CO during SA for CD. After an initial depression of CO by bolus phenylephrine in the current trial, a gradual recovery of CO was observed during a period of sustained increase in MAP and SVR, and decrease in HR (fig. 2A). The associated increase in SV (fig. 2B) could represent the Anrep effect, which is a positive inotropic effect that occurs during an increase in left ventricular afterload.[14]

Current literature supports the fact that the use of ephedrine as a vasopressor during elective CD under SA is associated with significantly more neonatal acidosis than phenylephrine.[15] In keeping with this literature, umbilical arterial pH was lower, and base excess was statistically significantly lower in patients receiving ephedrine predelivery in the current study (table 2). The clinical significance remains unknown.

In the twenty patients randomized to receive oxytocin or a mixture of oxytocin and 80 μg of phenylephrine, the hemodynamic responses to oxytocin were obtunded but not abolished (fig. 8, A and B). The fact that the onset of the hemodynamic effects of oxytocin was not prevented, together with the transient delayed depression of HR and CO after the administration of the mixture, suggest that the timing of the use of phenylephrine to obtund the hemodynamic effects of oxytocin, could be improved. SV remained stable when the mixture was used, once again suggesting the Anrep effect. These preliminary data suggest that further studies are required to establish the most effective doses and timing of com-

Table 5. Hemodynamic Data before and after Oxytocin or Mixture of Oxytocin and Phenylephrine

	Oxytocin (n = 10)		Oxytocin Plus Phenylephrine (n = 10)			95% Confidence Interval		
	Mean	SD	Mean	SD	Difference	Lower Limit	Upper Limit	*P** Value
Preoxytocin								
MAP	90.5	14.70	92.42	15.02	–1.95	–15.92	12.01	0.7724
SV	75.2	13.87	82.98	13.84	–7.83	–20.85	5.19	0.2223
SVR	1107.2	273.4	967.2	213.3	140.0	–90.36	370.43	0.2178
HR	86.0	15.40	90.54	13.49	–4.55	–18.15	9.06	0.4917
CO(LiDCO)	6.4	1.28	7.52	1.87	–1.13	–2.63	0.38	0.1331
CO(BioZ)	5.2	1.11	5.76	1.29	–0.56	–1.69	0.57	0.3086
Postoxytocin								
SV								
Peak	93.3	14.60	82.69	11.99	10.59	–1.96	23.14	0.0931
Percent-peak	26.1	20.99	0.79	14.48	25.33	8.39	42.27	0.0056
Time to peak	53.3	33.59	67.52	39.54	–14.21	–48.68	20.26	0.3978
SVR								
Peak	556.2	200.92	1329.00	354.29	–772.80	1043.00	502.20	<0.0001
Percent-peak	–45.8	38.26	41.24	34.93	–86.99	–119.80	–54.17	<0.0001
Time to peak	60.6	33.88	106.60	24.06	–45.98	–73.58	–18.37	0.0026
HR								
Peak	98.2	19.66	74.35	12.87	23.85	8.24	39.46	0.0049
Percent-peak	15.9	22.79	–16.37	19.42	32.27	12.38	52.16	0.0031
Time to peak	71.2	35.77	115.52	26.70	–44.32	–73.98	–14.67	0.0057
MAP								
Peak	63.9	10.90	93.11	16.10	–29.23	–42.15	–16.31	0.0002
Percent-peak	–28.9	9.92	2.99	22.11	–31.87	–47.97	–15.77	0.0002
Time to peak	43.4	7.45	86.89	27.32	–43.47	–62.28	–24.65	0.0006
CO(LiDCO)								
Peak	9.1	3.00	6.66	2.20	2.48	0.00	4.95	0.0496
Percent-peak	45.3	41.57	–9.33	28.88	54.64	21.01	88.27	0.0031
Time to peak	62.9	36.31	84.83	40.03	–21.97	–57.88	13.94	0.2150
CO(BioZ)								
Peak	6.4	1.64	6.16	1.91	0.26	–1.42	1.93	0.7494
Percent-peak	23.7	18.39	7.01	24.95	16.72	–3.87	37.32	0.1052
Time to peak	64.9	29.32	88.20	39.04	–23.30	–55.74	9.14	0.1486

* False discovery rate bound is 0.0057.

CO = cardiac output; CO(LiDCO) and CO(BioZ) = cardiac output derived using the LiDCO*plus* (LiDCO, Cambridge, United Kingdom) and BioZ (Cardio Dynamics International, San Diego, CA) monitors, respectively; HR = heart rate; MAP = mean arterial pressure; Peak = maximum absolute response to oxytocin or oxytocin plus phenylephrine; Percent-peak = percentage change in variable from preoxytocin value at peak value; SV = stroke volume; SVR = systemic vascular resistance.

binations of oxytocin and phenylephrine to eliminate the unwanted cardiovascular effects of oxytocin. Responses to 2.5 IU of oxytocin in the 32 patients receiving oxytocin alone are shown in figure 9. Similar trends were shown with the two CO monitors.

Lithium dilution CO (LiDCO) is a validated minimally invasive indicator dilution technique for the measurement of CO.[16] The LiDCO*plus* monitor is a beat-to-beat CO monitor that calculates SV from the arterial pressure waveform by using an autocorrelation algorithm. A recent editorial outlines the rationale for the use of this device in obstetric anesthesia research.[17] In the current study, specifically designed to examine short-term hemodynamic changes during SA for CD, bioimpedance changes were concurrently measured to corroborate the pulse wave form-derived data. Transthoracic electrical bioimpedance CO measurements are noninvasive and provide continuous real-time data. Using the Bioz device, based on the Sramek-Bernstein method, several studies have shown good correlation with thermodilution and Fick methods.[18] Several publications have reported useful trend measurements during CD, employing impedance cardiography.[19,20] Using the Bland and Altman approach, the limits of agreement between absolute values of CO derived from LiDCO*plus* and BioZ were outside the recommended acceptable 30%[21] in the current study. However, the agreement between the hemodynamic trends demonstrated by both LiDCO*plus* and BioZ in this study, in response to both vasopressors and oxytocin, provide further evidence of the usefulness of the pulse wave form monitor as a research tool for the study of acute hemodynamic changes during SA. The larger differences between the instruments in Group P (fig. 5), may reflect a tendency of bioimpedance methods to overestimate CO when SVR is high.[22] There was a difference between the two monitors in the time to peak effect after the administration of vasopressor. This may be a result of the fact that the LiDCO*plus* derives values

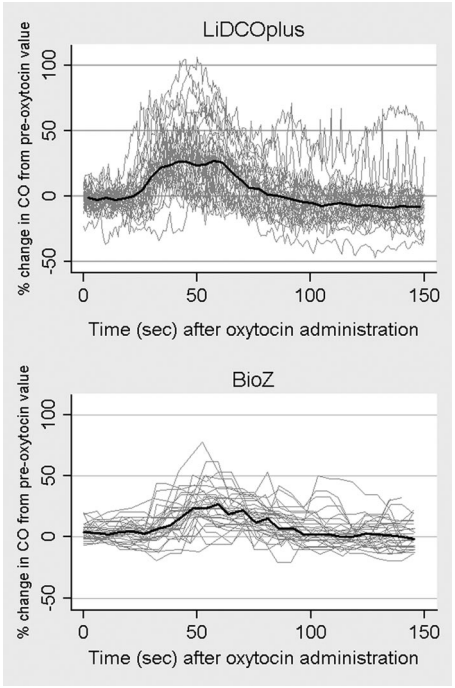

Fig. 9. Ensembles of changes in cardiac output as shown with each monitor in all patients receiving oxytocin alone (n = 32). The percentage change in cardiac output at peak effect was 32.7% (32.8%) *versus* 27.8% (18.9%) in the LiDCO*plus* (LiDCO, Cambridge, United Kingdom) and BioZ (Cardio Dynamics International, San Diego, CA) monitors, respectively. CO = cardiac output.

from the peripheral arterial trace, whereas the BioZ uses centrally measured changes in thoracic impedance. The sampling rate of the two devices was also different; the LiDCO*plus* sampled every heartbeat, and the BioZ sampled every 10 beats. These two effects probably account adequately for the difference in time intervals.

In conclusion, this study shows that bolus phenylephrine produced an absolute reduction in maternal CO and decreased CO when compared with ephedrine during elective SA for CD. CO changes correlated strongly with HR changes. HR may therefore be the best surrogate indicator of CO during SA for CD. During SA, hemodynamic changes were characterized by a reduction in SVR and a partial compensatory increase in CO. This suggests that low-dose phenylephrine, insufficient to cause marked MAP increases above baseline associated with sinus bradycardia, may be the most appropriate intervention for the initial management of hypotension in most cases to restore SVR and CO to baseline levels. Phenylephrine coadministered with oxytocin obtunded, but did not abolish, the unwanted hemodynamic effects of oxytocin after delivery. The agreement between the trends shown by the two CO monitors after both vasopressor and oxytocin administration lends further support to this form of pulse waveform analysis as a research tool.

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