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Hemodynamic Changes Associated with Spinal Anesthesia for Cesarean Delivery in Severe Preeclampsia

Robert A. Dyer, F.C.A. (S.A.), Jenna L. Piercy, F.C.A. (S.A.),† Anthony R. Reed, F.R.C.A.,† Carl J. Lombard, Ph.D.,‡ Leann K. Schoeman, F.C.O.G. (S.A.),§ Michael F. James, Ph.D.‖*

Background: **Hemodynamic responses to spinal anesthesia (SA) for cesarean delivery in patients with severe preeclampsia are poorly understood. This study used a beat-by-beat monitor of cardiac output (CO) to characterize the response to SA. The hypothesis was that CO would decrease from baseline values by less than 20%.**

Methods: **Fifteen patients with severe preeclampsia consented to an observational study. The monitor employed used pulse wave form analysis to estimate nominal stroke volume. Calibration was by lithium dilution. CO and systemic vascular resistance were derived from the measured stroke volume, heart rate, and mean arterial pressure. In addition, the hemodynamic effects of phenylephrine, the response to delivery and oxytocin, and hemodynamics during recovery from SA were recorded. Hemodynamic values were averaged for defined time intervals before, during, and after SA.**

Results: **Cardiac output remained stable from induction of SA until the time of request for analgesia. Mean arterial pressure and systemic vascular resistance decreased significantly from the time of adoption of the supine position until the end of surgery. After oxytocin administration, systemic vascular resistance decreased and heart rate and CO increased. Phenylephrine, 50 μg, increased mean arterial pressure to above target values and did not significantly change CO. At the time of recovery from SA, there were no clinically relevant changes from baseline hemodynamic values.**

Conclusions: **Spinal anesthesia in severe preeclampsia was associated with clinically insignificant changes in CO. Phenylephrine restored mean arterial pressure but did not increase maternal CO. Oxytocin caused transient marked hypotension, tachycardia, and increases in CO.**

ONLY since 1995, when the first randomized trial on the use of regional *versus* general anesthesia for cesarean delivery in severe preeclampsia was published,[1] has spinal anesthesia (SA) been considered an option in this high-risk group of patients. As recently as 1998, an editorial recommended that epidural anesthesia is preferable to SA for cesarean delivery,[2] even if the patient has not received epidural anesthesia in labor. Many recent studies suggest that SA is safe in the absence of contraindications to regional anesthesia.[3–6] Some studies have shown less hypotension and lower vasopressor requirements than during SA in healthy parturients. One investigation found less hypotension during SA in severe preeclamptics than in preterm women in whom fetal weights were similar.[4] This eliminated the possibility that the more minor degree of hypotension was due to a lesser degree of aortocaval compression in preeclamptic patients. Nevertheless, hypotension and placental underperfusion remain a risk,[7] and SA may be associated with more neonatal acidosis than general anesthesia.[8]

Most studies have used heart rate (HR) and blood pressure measurements as surrogate markers of maternal cardiac output (CO). Although pulse and blood pressure measurements are of value in assessing the safety of an anesthetic technique, the true goal of SA for cesarean delivery is to maintain maternal CO and uteroplacental blood flow. In healthy patients, the maximum change in CO has been shown to correlate better with uteroplacental blood flow than upper arm blood pressure.[9] Furthermore, in severe preeclampsia, an increased systemic vascular resistance (SVR) could render blood pressure a poor indicator of CO, but the information available on such patients during SA is scanty. It was therefore decided to investigate CO changes during SA for cesarean delivery in severe preeclampsia. Our hypothesis was that SA would result in a clinically insignificant change in CO in these patients, other than at the time of oxytocin administration. Also studied were the hemodynamic responses to vasopressors and to delivery and oxytocin. In addition, an assessment was made of the hemodynamics of recovery from SA.

Ultimately, a better understanding of the perioperative hemodynamic changes could contribute to a reduction in perioperative pulmonary edema, renal dysfunction, eclampsia, and neonatal morbidity.

Materials and Methods

Fifteen patients were recruited to this prospective observational study of the hemodynamics of SA for cesar-

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* Associate Professor, † Senior Specialist Anesthesiologist, ‖ Professor and Head, Department of Anesthesia, § Senior Specialist Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, University of Cape Town. ‡ Director, Biostatistics Unit, Medical Research Council, Cape Town, South Africa.

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Address correspondence to Dr. Dyer: D23 Department of Anesthesia, University of Cape Town and New Groote Schuur Hospital, Anzio Road, Observatory, Cape Town 7925, South Africa. robert.dyer@uct.ac.za.

ean delivery in severe preeclampsia. Preeclampsia was regarded as severe if the systolic blood pressure on admission exceeded 160 mmHg and/or the diastolic blood pressure exceeded 110 mmHg, obtained on at least two separate occasions, or if the patient had symptoms of imminent eclampsia (namely severe headache, visual disturbance, epigastric pain, hyperreflexia, dizziness and fainting, or vomiting) and proteinuria on urine dipstick was 3+ or worse. Patients with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome were eligible for inclusion if the platelet count exceeded 75×10^9/l.

The study commenced after the approval of the Human Research Ethics Committee of the University of Cape Town (Cape Town, Western Cape, South Africa). Informed written consent for inclusion in the study was taken at the time of decision to proceed to cesarean delivery. The decision to proceed with operative delivery for either a maternal or a fetal indication was made by the obstetric team independent of the investigators. Patients with severe preeclampsia, with worsening maternal disease, and requiring urgent but not emergency cesarean delivery were eligible for recruitment to the study.

Exclusion criteria were as follows: patient refusal, any contraindication to SA, body mass index greater than 35 kg/m^2, chronic hypertension, abruptio placentae, placenta praevia, coagulation abnormality, thrombocytopenia (platelet count $<75 \times 10^9$/l), local or generalized sepsis, cord prolapse, less than 28 weeks' gestation, twin pregnancy, active labor, or a nonreassuring fetal heart trace. Should any spinal anesthetic take longer than 30 min to perform, the patient would receive general anesthesia and be withdrawn from the study.

The antepartum management was according to the established protocol of our institution: On admission, all patients with severe preeclampsia have an intravenous line placed, and receive seizure prophylaxis consisting of magnesium sulfate as a loading dose of 4 g intravenously, followed by 1 g hourly. Volume expansion using 300–500 ml hydroxyethyl starch precedes the use of intravenous dihydralazine, followed by a balanced crystalloid solution administered at less than 120 ml/h. Dihydralazine is administered intravenously, either as 2.5-mg boluses or as a continuous infusion. If there is no immediate maternal or fetal indication for delivery and gestational age is less than 34 weeks, the patient is admitted for in-patient expectant management until an indication for delivery arises. Oral alpha-methyldopa and/or nifedipine are used for blood pressure control. However, if gestational age on admission is more than 34 weeks, delivery is expedited after stabilization of the mother. If cesarean delivery is anticipated, patients receive 30 ml sodium citrate orally in the operating room.

Noninvasive monitoring consisted of electrocardiograph and pulse oximetry. CO measurements used a beat-to-beat CO monitor that calculates stroke volume (SV) from the arterial pressure waveform using an autocorrelation algorithm (LiDCO*plus*; LiDCO, London, United Kingdom). The nominal SV is converted to actual SV by calibration with lithium dilution CO measurement. An extensive description of the theory behind the transformation has been previously reported.[10,11] A 20-gauge intraarterial line was inserted, and calibration of the CO monitor was performed. Because of time constraints, one calibration was performed in 5 cases, and two separate calibrations, 5 min apart, were performed in the remaining 10 patients. In these cases, the average calibration factor was calculated and applied to the data. Beat-by-beat HR; systolic, diastolic, and mean arterial pressure (MAP); SV; and CO were recorded in an Excel (Microsoft, Redmond, WA) workbook, from the time of calibration until the time of first request for analgesia. Of primary interest in this study was the change in CO in each individual patient. To evaluate the hypothesis that SA caused no clinically significant decrease in CO, a 20% decrease from baseline values was used as the clinical criterion.

Placement of a central venous line is not required clinically in most patients with severe preeclampsia. Therefore, central venous pressure (CVP) was given an arbitrary value of 5 mmHg, for the purposes of calculation of SVR. Baseline data were obtained *post hoc* by averaging all hemodynamic parameters over the 2–6 min after calibration, with the patient in the left lateral position. The MAP value for the purposes of calculation of target blood pressures for vasopressor administration was recorded as the mean of three consecutive readings not differing from one another by more than 10%, taken in the 3 min before sitting up for the induction of anesthesia.

The management of SA was as follows: Intravenous crystalloid cohydration (modified Ringer's lactate, 10 ml/kg) was rapidly administered *via* a 16-gauge peripheral line, initiated after cerebrospinal fluid appeared in the hub of the spinal needle. Thereafter, no further fluids were administered unless excessive hemorrhage occurred. All patients received 2.0 ml hyperbaric 0.5% bupivacaine, plus 10 μg fentanyl, administered at the L3–L4 interspace. After 20 s in the sitting position, patients were positioned supine, with 20° of left lateral tilt, to minimize aortocaval compression. Block height was assessed using cold sensitivity to ethyl chloride spray. All mothers received 40% oxygen by facemask until delivery.

Interventions were as follows: The first choice vasopressor was phenylephrine, administered by the anesthesiologist in response to HR and blood pressure changes, as is normal clinical practice during SA for cesarean delivery.

If MAP decreased by 20% from baseline, 50 μg phenylephrine was administered every minute until the blood pressure recovered to within 20% of the base-

line value. No vasopressor was given if MAP was greater than 110 mmHg. If MAP decreased by 30% from baseline, 100 μg phenylephrine was administered every minute until the blood pressure recovered to within 20% of baseline.

If CO did not increase by 5% above the pretreatment level when the target MAP had been reached, ephedrine boluses of 5 or 10 mg were administered thereafter, according to the same protocol as for phenylephrine, should further hypotension occur. If any patient required more than 50 mg ephedrine, this was interpreted as tachyphylaxis, and phenylephrine was used thereafter.

If HR decreased to less than 55 beats/min in association with hypotension (MAP decrease by 30% from baseline), 0.5 mg atropine and 10 mg ephedrine were administered, and the hemodynamic response was recorded.

After delivery, phenylephrine (50–100 μg) or ephedrine (5–10 mg) was administered to maintain MAP within 30% of baseline pressure.

Further interventions were as follows: Thirty seconds after delivery, 2.5 U oxytocin in 10 ml water was administered over a period of 30 s. No vasopressor was administered for up to 3 min after oxytocin, and no further intraoperative oxytocin was administered until the end of surgery, unless requested by the obstetrician in the case of uterine atony.

Intravenous cefazolin, 1 g, was given at the end of the surgical procedure. Intraoperative maternal blood loss was estimated from suction bottle measurement and checking of swabs. Neonatal Apgar scores, umbilical arterial and maternal pH and base deficit, and neonatal weights were recorded.

Statistical Analysis

Hemodynamic values were averaged for the following defined time intervals:

1. Baseline measurements
2. Sitting (time from sitting up for SA until induction of SA)
3. Spinal anesthesia (from induction of SA until the adoption of the supine position)
4. Supine (from the return to the supine position until left lateral tilt)
5. Left lateral tilt (from tilt until skin incision)
6. Skin incision (from skin incision until 30 s before uterine incision)
7. Uterine incision (30-s time period before uterine incision)
8. Postdelivery (the 30-s period from delivery until administration of oxytocin)
9. Peak oxytocin effect (from administration of oxytocin until peak effect on CO)
10. End of surgery (30-s time period before skin closure)
11. Recovery from SA (5-min time period before request for analgesia)

These absolute values were analyzed for differences from baseline using analysis of variance for repeated measures with the Dunnett correction for multiple comparisons.

Cardiac output was the main outcome variable considered for testing the hypothesis that this hemodynamic variable did not deviate by more than 20% from the baseline value in the individual case. For the testing of this hypothesis, the period of oxytocin administration was excluded. Descriptive statistics of the cardiac variables were calculated for the 11 time periods considered. For CO, a regression model was used to estimate the mean change from baseline to each of the follow-up time intervals. This model took into account the repeated measurements within each patient by allowing a general variance–covariance structure to be estimated for this purpose. The 95% confidence intervals for the nine differences were adjusted to ensure an overall type I error rate of 5%. This was done using the Dunnett adjustment for multiple comparisons of *P* values and confidence intervals.

The mean changes from baseline values of the other cardiac variables were estimated using the same approach as for CO. The individual CO time profiles were plotted as well as the individual percentage change from baseline. The estimated changes from baseline values at each time interval with the adjusted 95% confidence intervals were also plotted. The Fisher exact test was used to test for an association between the indicator of a decrease of more than 20% in CO at any time point for all patients, and the time indicator variable.

The effects of phenylephrine on each hemodynamic parameter were measured by averaging the effects before and after each dose in each patient, and then averaging between patients. Prevalues were taken as the mean value for the period 30 s before phenylephrine administration. Postvalues were taken as the mean value for the 5 s before and after the highest value recorded in the 3 min after vasopressor administration. A similar procedure was followed to estimate the hemodynamic changes from baseline that had occurred at the time immediately preceding the first administration of phenylephrine (*i.e.*, at target MAP). The postphenylephrine values were then compared to the prephenylephrine values using repeated-measures analysis of variance.

The response to oxytocin was analyzed as follows: hemodynamic data were averaged for 30 s before the administration of oxytocin. As for phenylephrine, 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. This value was then compared with the preoxytocin value using analysis of variance for repeated measures. Data analysis was performed using SAS version 9 (SAS Institute Inc., Cary, NC).

Table 1. Demographic Data, Relevant Preoperative Drug Therapy, and Baseline MAP

Case No.	Gravidity	Parity	Age, yr	Weight, kg	Height, cm	GA, wk	Relevant Preoperative Drugs	MAP, mmHg
1	1	1	26	80	154	33	Mg, nifedipine	139
2	2	2	27	77	161	36	Mg, nifedipine	147
3	1	0	28	79	162	32	Mg, nifedipine	138
4	4	3	40	81	163	31	Mg, nifedipine, dihydralazine, α-methyldopa	133
5	1	0	23	70	160	28	Mg, nifedipine, α-methyldopa	142
6	1	0	24	102	162	33	Mg, nifedipine, dihydralazine, α-methyldopa	132
7	2	1	25	100	174	31	Mg, dihydralazine	130
8	2	1	30	70	172	37	Nil	135
9	2	1	28	90	160	34	Nifedipine, α-methyldopa	125
10	3	2	26	69	151	33	Mg, α-methyldopa	135
11	3	1	25	77	155	33	Nifedipine, α-methyldopa	138
12	2	1	24	70	141	32	Mg, nifedipine, α-methyldopa	100
13	1	0	28	60	148	29	Mg, dihydralazine, nifedipine, α-methyldopa	110
14	1	0	28	94	155	34	Nifedipine	128
15	2	1	24	60	156	34	Mg, dihydralazine	85

GA = gestational age; Mg = magnesium sulfate; MAP = mean arterial pressure used for calculating target pressure for vasopressor administration (MAP-20%).

Results

Fifteen consecutive patients meeting the entry criteria were recruited over a period of 14 months. Two patients did not consent. Recruitment took place from November 2005 to January 2007 at the Maternity Centre of Groote Schuur Hospital, Cape Town, South Africa. Demographic data, relevant preoperative drug therapy, and MAP used to calculate the target for vasopressor administration are shown in table 1.

Seven patients had had a previous cesarean delivery, and four had deteriorating renal function evidenced by an increased serum creatinine level. The remainder had worsening maternal disease with difficult control of blood pressure.

The median maximum block height was T3 (range, T3–T4), and the block height at the time of request for analgesia was T8 (range, T5–T10). The mean time (SD) for completion of fluid infusion was 12.5 (2.6) min. In no patient was estimated blood loss greater than 600 ml. The mean time (SD) from induction of SA until request for analgesia was 114.5 (31.1) min. There were no block failures. Only two patients had symptoms during the surgical procedure; one had headache, and the other had blurred vision and epigastric pain.

Averaged hemodynamic variables at the defined time intervals are shown in table 2.

Cardiac output remained stable throughout cesarean delivery and until the time of request for analgesia in each patient, except for the period after oxytocin administration (fig. 1A). Figure 1B illustrates CO percentage changes in individual cases, excluding the peak oxytocin effect. There were a total of 135 time epochs after the baseline period, of which 2 showed a greater than 20% decrease in CO. The two observed decreases were transient and the patients were asymptomatic. CO increased to more than 20% above baseline values in several cases at various time intervals. Assuming that the 135 time periods at which CO was measured were independent

Table 2. Hemodynamic Variables with Duration of Time Intervals for All Patients (n = 15)

	Mean Duration, s	HR, beats/min	MAP, mmHg	SV, ml/beat	CO, l/min	SVR, dyn · s · cm^{-5}
Baseline	120–360	82.5 (11.8)	125.8 (14.9)	76.2 (17.8)	6.2 (1.4)	1,633 (306)
Sitting	437 (181)	91.2 (14.6)*	132.5 (16.1)*	70.5 (15.4)	6.3 (1.3)	1,678 (272)
Spinal	59 (16)	94.1 (19.2)*	127.6 (16.8)	69.1 (17.6)*	6.3 (1.5)	1,627 (336)
Supine	35 (11)	94.5 (19.8)*	121.7 (15.5)*	77.4 (19.1)	7.1 (1.7)*	1,378 (262)*
Lateral tilt	439 (151)	83.5 (15.2)	114.0 (17.6)*	81.0 (19.9)*	6.6 (1.5)	1,364 (256)*
Skin incision	233 (115)	80.9 (15.5)	112.1 (17.2)*	81.4 (16.2)	6.5 (1.5)	1,368 (289)*
Uterine incision	30	81.6 (15.5)	110.8 (21.3)*	79.2 (16.1)	6.4 (1.5)	1,363 (298)*
Postdelivery	30	84.7 (12.6)	114.3 (15.0)*	82.9 (15.9)*	7.0 (1.5)*	1,295 (252)*
Oxytocin peak	45 (14)	101.5 (15.9)†	80.6 (15.3)†	89.1 (17.3)	9.1 (2.3)†	718 (282)†
End surgery	30	79.5 (11.3)	102.3 (13.6)*	80.1 (17.9)	6.3 (1.3)	1,286 (279)*
Recovery	300	71.6 (11.2)*	122.1 (10.1)	80.7 (19.3)	5.7 (1.2)*	1,725 (365)

Data are shown as mean (SD). For baseline values, the range of time is shown. Mean duration refers to the duration of the defined time interval. Time intervals defined in the protocol do not have SD indications. For oxytocin, the duration is the mean time from intravenous injection to peak effect on cardiac output (CO). All other hemodynamic indices are calculated at this time point.

* Significant difference from baseline values ($P < 0.05$). † Significant difference from all other time intervals ($P < 0.01$).

HR = heart rate; MAP = mean arterial pressure; SV = stroke volume; SVR = systemic vascular resistance.

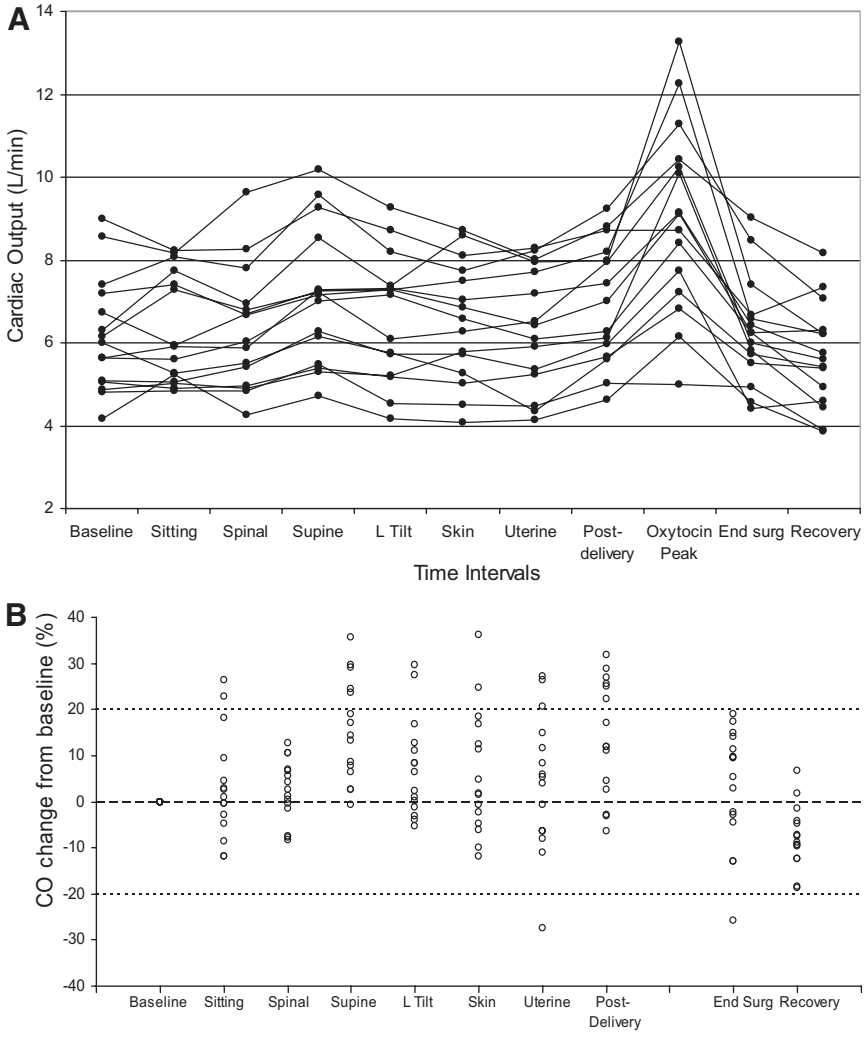

Fig. 1. (*A*) Cardiac output measurements for each patient at each time interval. Baseline = baseline measurements averaged after calibration of cardiac output monitor; sitting = time from sitting up for spinal anesthesia until induction of spinal anesthesia; spinal = time from induction of spinal anesthesia until patient supine; supine = time from adoption of supine position until left lateral tilt; L tilt = left lateral tilt (from tilt until skin incision); skin = time from skin incision until 30 s before uterine incision; uterine = 30-s time period before uterine incision; postdelivery = 30-s period from delivery until administration of oxytocin; oxytocin peak = time from administration of oxytocin until peak effect on cardiac output; end surg = 30-s time period before skin closure (end of surgery); recovery = 5-min time period before request for analgesia. (*B*) Percentage cardiac output (CO) change from baseline for individual patients, at defined time intervals, as in *A*. Reference lines have been drawn at + and −20%.

measurements, and considering the test for the association between the indicator for a CO decrease of more than 20% from baseline and the time indicator, a Fisher exact test indicated no significant association (P = 1.000).

Mean changes from baseline values in HR, MAP, SV, CO, and SVR, together with 95% confidence intervals at all time intervals, for the cohort of 15 patients, are shown in figures 2A–E.

Figure 3 shows ensembles of the responses of the 15 patients to oxytocin (HR, MAP, SV, CO, and SVR). Individual responses are shown as thin gray lines, and the ensemble average is depicted as a superimposed thick black line.

A total of 10 patients received phenylephrine, 8 before and 6 after delivery. The median (range) doses before and after delivery were 50 (0–150) and 0 (0–150) μg, respectively. Seven patients required ephedrine, and 1 developed tachyphylaxis, necessitating a change to phenylephrine, as dictated by the protocol. The median (range) dose of ephedrine was 0 (0–45) mg. Vasopressor use is summarized in table 3.

Immediately before the first administration of phenylephrine, *i.e.*, when MAP was 20% below baseline values, SVR was significantly lower than baseline measurements. CO and HR were not different from baseline at this time (table 4). The administration of phenylephrine was associated with a significant increase in MAP and SVR, and a significant decrease in HR, but SV and CO were not significantly changed from values immediately before phenylephrine use (table 5). There was a trend toward a decrease in CO. The mean (SD) times to peak effect of the first, second, and third doses were 28.3 (4.2), 39.6 (30.0), and 24.6 (3.2) s, respectively. The infrequent use of ephedrine precluded a detailed analysis of the use of this vasopressor.

Data relevant to the neonate include the following: The mean (SD) uterine incision to delivery time was 54.4 (29.2) s. The mean (SD) neonatal weight was 1,697 (520) g. The median (range) Apgar score at 1 min was 9 (7–9), and that at 5 min was 9 (9–10). The median (range) umbilical arterial pH and mean (SD) base deficit were 7.28 (7.19–7.31) and −3.1 (1.9) mM, respectively.

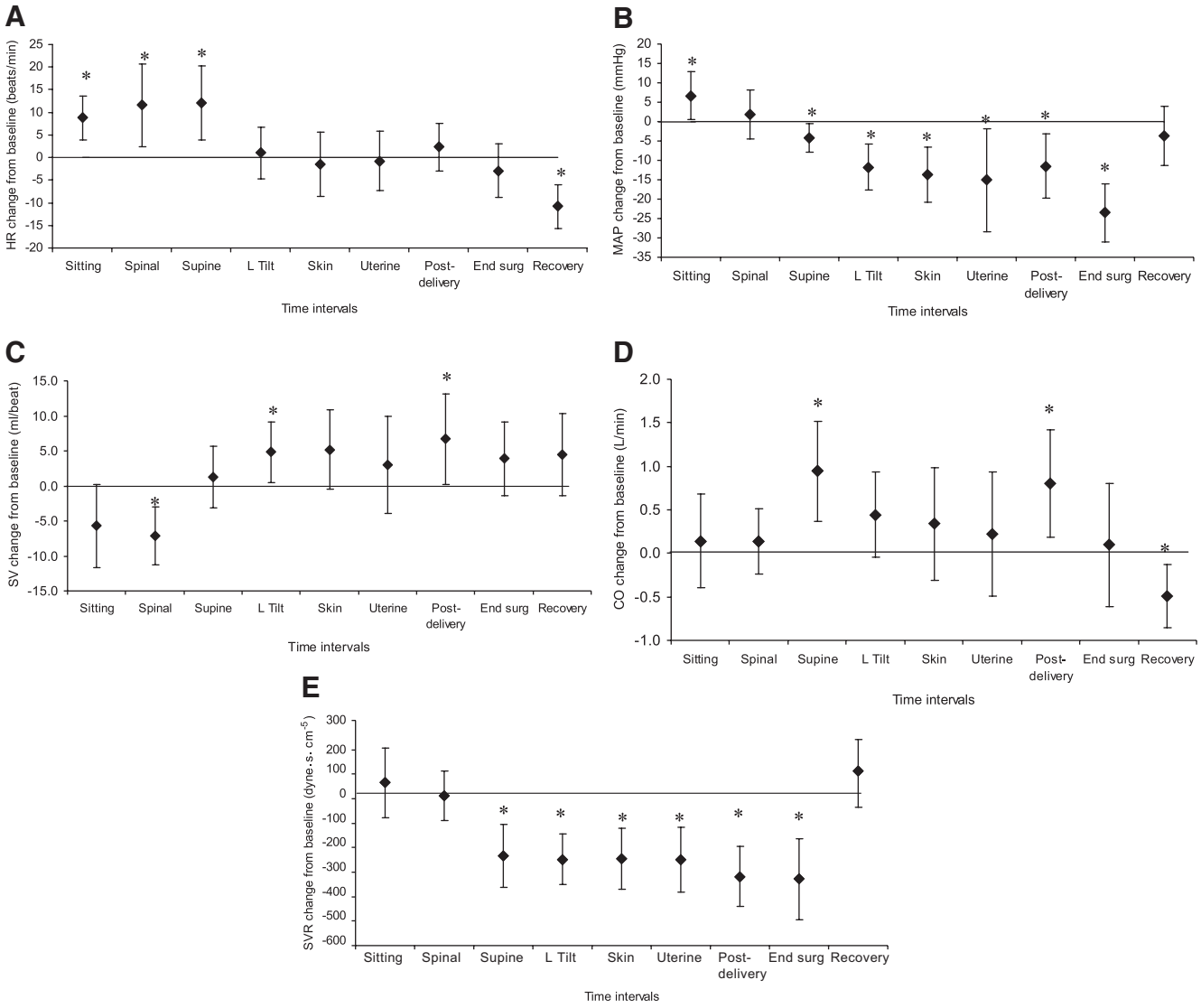

Fig. 2. Mean absolute changes from baseline values for all hemodynamic variables at defined time intervals, as in figure 1. (*A*) Heart rate (HR). (*B*) Mean arterial pressure (MAP). (*C*) Stroke volume (SV). (*D*) Cardiac output (CO). (*E*) Systemic vascular resistance (SVR). *Error bars* indicate 95% confidence intervals. * $P < 0.05$.

Discussion

This observational study describes the maternal hemodynamic response to SA for cesarean delivery in 15 patients with severe preeclampsia, using phenylephrine as the first choice vasopressor, as is the current practice in healthy patients during SA for cesarean delivery.[12,13] SA was associated with hemodynamic stability in the 15 patients studied (fig. 1A); therefore, this study confirms the hypothesis that CO decreases were clinically insignificant during the procedure. During only two time intervals out of a total of 135 comparisons with baseline values, in two different patients, did CO decrease by more than the clinically relevant value of 20% of baseline measurements (fig. 1B). The mean baseline SVR was above normal despite antihypertensive therapy, and the mean baseline CO was in the normal range (table 2), in keeping with previous literature relating to the hemodynamics of treated patients with severe preeclampsia.[14] Induction of SA was followed by significant decreases in MAP and SVR, which persisted until the end of surgery. In many patients, CO increased to more than 20% above baseline values at several time intervals other than at the time of peak oxytocin effect (figs. 1B and 2D). Therefore, the main hemodynamic effect of SA was modest afterload reduction. The use of phenylephrine was associated with a trend toward a decrease in CO. Although CVP was not measured, the magnitude of the arterial pressure changes suggests that an increase in afterload contributed to the mechanism (table 5).

The requirement for vasopressors was low, in keeping with the existing literature, which suggests a lower requirement than in normal parturients.[3–5] One recent publication has recommended that phenylephrine be infused in normal parturients during SA for cesarean

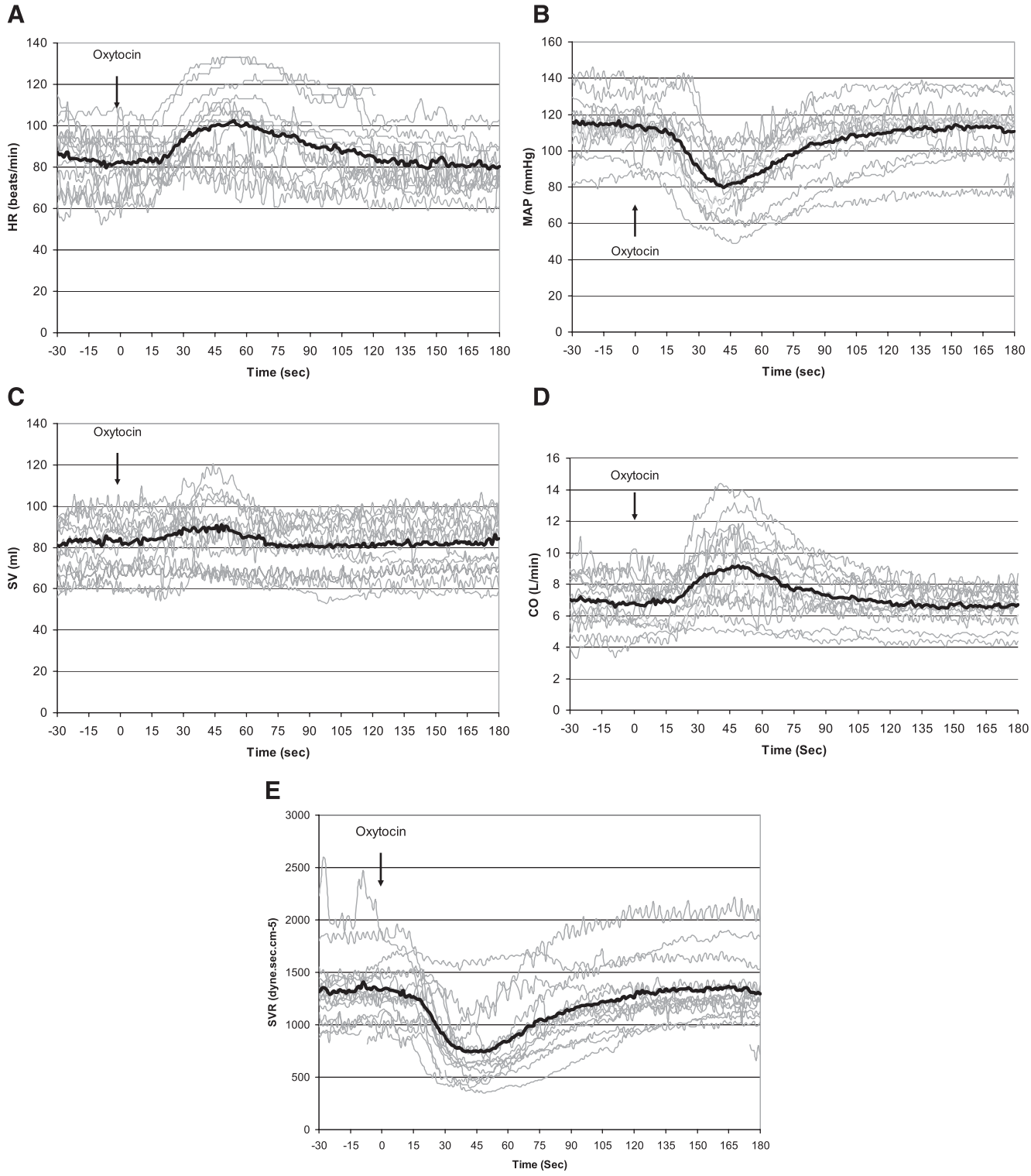

Fig. 3. Ensemble of hemodynamic changes after the administration of oxytocin. (*A*) Heart rate (HR). At peak effect, HR increased from 84.7 (12.6) to 101.5 (15.9)* beats/min. (*B*) Mean arterial pressure (MAP). At peak effect, MAP decreased from 114.3 (15.0) to 80.6 (15.3)* mmHg. (*C*) Stroke volume (SV). At peak effect, SV increased from 82.9 (15.9) to 89.1 (17.3) (not significant). (*D*) Cardiac output (CO). At peak effect, CO increased from 7.0 (1.5) to 9.1 (2.3)* l/min. (*E*) Systemic vascular resistance (SVR). At peak effect, SVR decreased from 1,295 (252) to 718 (282)* dyn · s · cm^{-5}. * Value significantly different from baseline and postdelivery; $P < 0.01$.

delivery at a rate that maintains baseline MAP.[12] However, this technique was associated with a 47% incidence of hypertension. In the current study, when target values of MAP for vasopressor administration (a 20% decrease in blood pressure) were reached, CO had not decreased significantly, and in many cases had increased (table 4). This suggests that maintaining blood pressure at the baseline level in this patient population during SA may

Table 3. Vasopressor Administration Predelivery and Postdelivery

Patient No.	Phenylephrine Predelivery, μg	Phenylephrine Postdelivery, μg	Ephedrine Predelivery, μg	Ephedrine Postdelivery, μg
1	0	150	0	0
2	0	0	0	0
3	0	0	0	0
4	50	0	10	0
5	50	50	0	5
6	50	100	0	15
7	0	0	0	0
8	50	0	5	0
9	0	0	0	0
10	0	50	0	0
11	0	0	0	0
12	50	0	0	0
13	50	150	5	45
14	100	50	10	5
15	50	0	5	0

not be optimal practice, especially considering the risk of worsening hypertension in patients with severe preeclampsia. Furthermore, phenylephrine, administered in response to a 20% decrease in baseline MAP, did not increase CO. In several cases, CO decreased (table 5). The mean change in CO was not significant, but this could reflect problems of statistical power.

Oxytocin is known to have complex cardiovascular effects leading to hypotension, mediated *via* several mechanisms. These include effects on cardiac oxytocin receptors, release of nitric oxide in the peripheral vasculature, and release of atrial and brain natriuretic peptide.[15] A small dose of oxytocin (2.5 U), administered 30 s after delivery, was associated with significant hypotension and increases in HR, SV, and CO (fig. 3). These transient hemodynamic effects were greater in these patients with severe preeclampsia than those after the sympathectomy associated with SA. The response to oxytocin was more pronounced than in a recent study using thoracic bioimpedance technology in healthy parturients, where 5 or 10 U oxytocin was administered as a rapid bolus.[16] In patients not at risk for uterine atony, the

Table 4. Hemodynamic Data at Baseline and before First Administration of Phenylephrine in Patients Who Received the Vasopressor (n = 10)

	Baseline, Mean (SD)	Pre P1, Mean (SD)	Estimated Change	99% CI
CO, l/min	6.1 (1.7)	6.3 (1.5)	0.2	−1.0 to 1.4
SVR, dyn · s · cm^{-5}	1,616 (362)	1,198 (330)	−418	−628 to −208
MAP, mmHg	122 (17)	95 (13)	−27	−34 to −21
SV, ml/beat	76.9 (19.5)	76.0 (19.7)	−0.9	−7.8 to 6.0
HR, beats/min	80.4 (11.6)	84.0 (16.1)	4.4	−7.2 to 16.0

99% confidence intervals (99% CIs) were used to adjust for multiplicity. There were significant decreases in systemic vascular resistance (SVR) and mean arterial pressure (MAP).

CO = cardiac output; HR = heart rate; pre P1 = values before the first dose of phenylephrine; SV = stroke volume.

Table 5. Effects of Phenylephrine on Hemodynamic Parameters Using Data from All Doses of Phenylephrine (n = 20)

	Pre, Mean (SD)	Post, Mean (SD)	Estimated Change	99% CI
CO, l/min	6.3 (1.5)	5.8 (1.6)	−0.5	−1.1 to 0.2
SVR, dyn · s · cm^{-5}	1,155 (297)	1,507 (469)	352	59 to 645
MAP, mmHg	91 (13)	108 (15)	17	8 to 24
SV, ml/beat	75.9 (18.7)	78.7 (20.5)	2.8	−2.4 to 8.1
HR, beats/min	84.2 (15.1)	74.9 (10.8)	−9.3	−17.2 to −1.4

Heart rate (HR) decreased significantly, and mean arterial pressure (MAP) and systemic vascular resistance (SVR) increased significantly after phenylephrine administration.

CI = confidence interval; CO = cardiac output; pre = averaged values before phenylephrine; post = averaged values after phenylephrine; SV = stroke volume.

ED_{90} for oxytocin has been found to be 0.35 U.[15] A repeat of this study would be useful in high-risk patients such as those with severe preeclampsia. In the interim, our data suggest that oxytocin is probably best administered by slow infusion in these patients during SA.

In a recent study using whole body impedance cardiography during SA for cesarean delivery, the authors reported on 10 preeclamptic women, of whom 6 had severe disease.[17] Comparative hemodynamic data from healthy women were obtained from historic rather than contemporaneous studies.[18] Patients received a preload of 10 ml/kg hydroxyethyl starch, 6%, and 10 ml · kg^{-1} · h^{-1} thereafter. Fluid preloading increased CO in the preeclamptic group, but not in healthy patients. The use of ephedrine increased both MAP and SVR. At delivery, increases in the CO of preeclamptic patients were due only to increases in HR; SV did not increase, in contrast with the healthy patients. The effects of oxytocin were not described. Of particular clinical relevance was the finding that in the healthy patients, hemodynamic values returned to baseline levels after recovery from SA, whereas the stroke index and cardiac index in the preeclamptic group were significantly lower than presurgery levels. The authors speculate that the inability to increase SV at delivery in the preeclamptic group could be due either to the existence of a lower preload after delivery than in healthy patients or to diastolic dysfunction resulting in an inadequate adaptation to volume load at delivery. Such changes could predispose these patients to life-threatening pulmonary edema in the early puerperium. In the current study, delivery and oxytocin administration were associated with CO changes that were predominantly HR mediated (fig. 3). SV was not significantly different from baseline values at the time of peak oxytocin effect. At the time of recovery from SA, CO was significantly lower than baseline values. However, the magnitude of the effect was only 0.49 l, which is well below criteria for a clinically relevant decrease, namely 20% of baseline values, or 1.23 l. This decrease in

CO is most likely attributable to the significant decrease in heart rate at this time (fig. 2A).

Lithium dilution cardiac output (LiDCO) is a minimally invasive indicator dilution technique for the measurement of CO.[19] CO is derived from the dilution curve generated by a lithium-sensitive electrode attached to the arterial line. Compared with thermodilution, lithium dilution has shown closer agreement in clinical studies with electromagnetic flow measurement.[19] Only peripheral arterial and venous cannulation is required.[20] A small dose of lithium chloride is injected as an intravenous bolus. A single lithium chloride determination at 0.3 mmol is the equivalent to a steady state plasma lithium concentration of 1/240 of the therapeutic level. The LiDCO*plus* monitor is a beat-by-beat CO monitor that calculates SV from the arterial pressure waveform using an autocorrelation algorithm. The algorithm is not dependent on waveform morphology, but calculates nominal SV from a pressure–volume transform of the entire waveform. The nominal SV is converted to actual SV by calibration of the algorithm with the lithium dilution method. Two recent studies have confirmed good agreement between continuous CO measurement using this monitor calibrated with lithium dilution, and thermodilution or lithium dilution.[21,22] In these studies, measurements remained reliable without recalibration for at least 8 h. In two studies, there was also good agreement with the thermodilution method.[10,21] The LiDCO*plus* monitor was regarded as the most appropriate for the current study.

Sudden decreases in SVR could result in a change in CO measurement bias. In a recent validation study of the monitor used in the current study, which examined this issue, a decrease in SVR resulted in decreased CO readings relative to the reference method, in that case lithium dilution. The authors reported that a decrease in SVR of 600 dyn $\cdot$ s $\cdot$ cm^{-5} predicted an increase in the CO measurement bias of less than 1 l/min.[22] This suggests that the cardiovascular response to oxytocin in the current study may represent an underestimate of the true changes, but this may be of statistical rather than clinical significance.

Because CVP was not measured in this study, a default CVP of 5 mmHg was chosen for the purposes of calculation of SVR. Because right atrial pressure is much lower than systemic pressure, this does not impact significantly on the calculation of SVR. Furthermore, in a previous study using CVP measurements before and during SA for cesarean delivery in preeclampsia, a preload of 1 l crystalloid induced a transient mean increase of less than 5 mmHg, and CVP values returned toward baseline after induction of SA.[7] Modest crystalloid cohydration was used in the current study, because there may be advantages in administering fluids immediately after induction of SA, thus limiting acute CVP increases and the effects of rapid redistribution of crystalloid fluid.[12,23]

More than 800 patients with severe preeclampsia were admitted during the time period of recruitment to the study (14 months). The slow recruitment was due to two factors. First, obstetricians in our institution favor induction of labor at 34 weeks' gestation, in the absence of a previous maternal or fetal indication for cesarean delivery. Therefore, a relatively small percentage of patients undergo cesarean delivery for a maternal indication. Second, in the great majority of patients with severe preeclampsia requiring cesarean delivery in our institution, the indication is a nonreassuring fetal heart trace. The delays in establishing and calibrating noninvasive CO monitoring would not be ethically justifiable in these patients. In view of the fact that only approximately 50% of patients require a vasopressor before delivery, a large cohort of patients and a prolonged time period of investigation would be required for adequate power in a randomized trial on the effects of phenylephrine and ephedrine on maternal and fetal outcome.

In conclusion, this observational study in 15 patients with severe preeclampsia showed that SA was associated with modest afterload reduction and minimal CO changes. Phenylephrine did not improve CO, and further work is required to establish whether a mixed α, β agonist is the preferred vasopressor, from both the maternal and the fetal point of view, because no observations were made in the current study regarding uteroplacental perfusion. Oxytocin causes transient profound hypotension, tachycardia, and an increase in CO, and these data suggest that consideration should be given to administering this drug by slow intravenous infusion. SV was well preserved at the time of recovery from SA, and there was a clinically insignificant decrease in CO at this time. Combined spinal–epidural anesthesia has been successfully used for cesarean delivery in patients with severe preeclampsia[24,25] and may confer benefits in terms of postoperative analgesia, but our data suggest that adequate hemodynamic stability, as assessed by CO changes, is provided by single-shot SA.

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