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ORIGINAL ARTICLE

Relationship between changes in regional cerebral blood volume and oxygenation and changes in cardiac output and systemic vascular resistance during spinal anesthesia in women undergoing cesarean section

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Abstract

Purpose The decrease in maternal regional cerebral blood volume (rCBV) and oxygenation (rCBO) during spinal anesthesia for cesarean section depends on the severity of hypotension. We examined the relationships between changes in the systemic circulatory parameters, cardiac output (CO) and systemic vascular resistance (SVR), and rCBV and rCBO after induction of spinal anesthesia, evaluated by near-infrared spectroscopy (NIRS) and an arterial pressure-based cardiac output monitoring system (APCOs).

Methods Seventeen patients undergoing elective cesarean section under spinal anesthesia were monitored every 1 min for mean arterial pressure (MAP), heart rate (HR), end-tidal carbon dioxide ($EtCO_2$) and oxygen saturation (SpO_2), and at 20 s intervals for CO, SVR, concentrations of oxy-hemoglobin (Hb), deoxy-Hb, total-Hb, and tissue oxygenation index (TOI), until 15 min after the intrathecal injection of bupivacaine. We investigated changes in the parameters from baseline and evaluated correlations between the changes in total-Hb and TOI and changes in CO and SVR, respectively, at the same timepoints.

Results Oxy-Hb, total-Hb, TOI, and SVR significantly decreased and HR significantly increased with a decrease in MAP ($P<0.01$). Deoxy-Hb, CO, SpO_2, and $EtCO_2$ levels did not change from baseline. There were statistically significant, although weak, positive correlations between both total-Hb and TOI with SVR (total-Hb; $r=0.18$, $P<0.01$, TOI; $r=0.38$, $P<0.01$).

Conclusion The decreases in both rCBV and rCBO after induction of spinal anesthesia for cesarean section are probably dependent on the decrease in SVR due to spinal anesthesia.

Keywords Near-infrared spectroscopy · Cerebral blood volume and oxygenation · Cardiac output · Systemic vascular resistance

Introduction

During cesarean section, potent sympathetic blockade after spinal anesthesia frequently produces maternal hypotension, which may cause not only fetal acidemia [1], but also adverse maternal symptoms, such as nausea and vomiting [2, 3]. The adverse maternal symptoms are believed to be related to cerebral ischemia secondary to hypotension [2, 4]. In fact, the previous studies using near-infrared spectroscopy (NIRS) reported significant decrease in the indices of regional cerebral blood volume (rCBV; total-Hb) and oxygenation [rCBO; rSO_2 and tissue oxygenation index (TOI)] after induction of spinal anesthesia [5–7]. We also previously demonstrated that decreases in both total-Hb and TOI after induction of spinal anesthesia are related to the severity of hypotension [2]. Other previous studies using non- or low-invasive hemodynamic monitoring systems demonstrated that systemic vascular resistance (SVR) decreased simultaneously with decrease in blood pressure, but cardiac output (CO) did not decrease after spinal injection [8–10]. Taking the above into consideration, the reductions in rCBV

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and rCBO after induction of spinal anesthesia may depend on decrease in SVR, and not on decrease in CO. However, the relationships between changes in systemic circulatory parameters (CO and SVR) and changes in rCBV and rCBO have not been identified.

This is the first study to investigate the contributions of CO and SVR during spinal anesthesia for cesarean section to changes in rCBV and rCBO, simultaneously using both NIRS and an arterial pressure-based cardiac output system (APCOs). We hypothesized that both the decrease in rCBV and rCBO after induction of spinal anesthesia would be closely related to decrease in SVR, but not to decrease in CO.

Materials and methods

This prospective, observational study was approved by the Hospital Ethics Committee on Human Rights in Clinical Trials and Research of Nihon University Hospital (RK-150714-5), and was registered in the UMIN Clinical Trials Registry (ID: 000019862). Written informed consent was obtained from all patients participating in this clinical trial.

Subjects

Twenty full-term pregnant patients with placenta previa, triplets or placenta accreta, aged 20 years and older, American Society of Anesthesiologists (ASA) grade I or II, scheduled for cesarean section under spinal anesthesia, were included in this study. Exclusion criteria included hypertension, diabetes, and renal dysfunction due to pregnancy, anemia (hemoglobin concentration < 10 g/dL), and obesity (body mass index > 30 kg/m^2).

Anesthetic procedure

All patients fasted overnight and did not receive any premedication. On arrival at the operating room, all patients were monitored using ECG electrodes, an arm cuff on the right upper arm for non-invasive blood pressure measurements, pulse oximeter (SpO_2) on the fingertip, a sampling tube for end-tidal CO_2 ($EtCO_2$) placed in the lower part of the nostril, and an NIRS probe on the left forehead. Furthermore, a 22-gauge catheter was inserted into the left radial artery under local anesthesia to measure CO and SVR using APCOs. Patients were placed in the supine position, with the operating table tilted 15° to the left. Subsequently, patients were started on oxygen inhalation at 3 L/min through a face mask, in addition to being administered a hydroxyethyl starch solution (HES, 6%), 20 mL/kg/h (maximum 1000 mL). After oxygenation for 3 min, baseline values of mean arterial pressure (MAP), heart rate (HR), SpO_2, $EtCO_2$, CO and SVR, and the NIRS parameters of concentrations of oxy-hemoglobin (Hb), deoxy-Hb, total-Hb (oxy-, deoxy-, and total-Hb were zeroed) and TOI were recorded. Spinal anesthesia and epidural catheterization were performed with the patients in the right lateral decubitus position. An epidural catheter was inserted at the Th12-L1 intervertebral space, and subarachnoid puncture was performed at the L3–4 intervertebral space. Hyperbaric 0.5% bupivacaine was used for spinal anesthesia in all patients, the dose being determined by the individual anesthetist. Immediately after intrathecal injection of bupivacaine, the patients were returned to the supine position with a 15° tilt to the left. Hypotension, which was defined as MAP $< 80\%$ of the baseline value or systolic blood pressure of < 90 mmHg, was treated with a 4 mg bolus of ephedrine if the patient's HR (beats/min) was less than 80, or with a 50-μg bolus of phenylephrine if the patient's HR was 80 and above. Ten minutes after induction of spinal anesthesia, the pinprick test was performed to assess the adequacy of anesthesia, and patients whose analgesia level was limited to below the Th10 level were excluded from the study.

Monitoring

MAP, HR, SpO_2, $EtCO_2$, and respiratory rate (RR) were monitored every 1 min (BP-608 Evolution II™, OMRON Colin, Tokyo, Japan). The data of patients whose RR was more than 25 breaths/min during the experiment were excluded. Changes in rCBV and rCBO, estimated from total-Hb and TOI, respectively, were measured at the forehead using NIRS (NIRO-200NX™, Hamamatsu Photonics, Hamamatsu, Japan). With this system, NIR light from three laser diodes (735, 810 and 850 nm) is directed at the head through a fiberoptic bundle, and the reflected light is transmitted to a multisegment photodiode detector array. The NIRS system measures concentrations of oxy-Hb, deoxy-Hb, total-Hb (total-Hb = oxy-Hb + deoxy-Hb), and the TOI. Each parameter was continuously measured and the data were recorded every 20 s throughout the study. Changes in CO and SVR were continuously measured by APCOs (Vigileo-FloTrac™ system, Edwards Lifesciences, Irvine, CA, USA). This system measures CO using arterial pressure waveform analysis and considering the patient's age, gender, height and weight data, and calculates SVR in accordance with the algorithm: $SVR\ (dynes \times s/cm^5) = MAP/CO \times 80$. The mean change in CO and SVR every 20 s are displayed and recorded by the device.

Data analysis

The primary outcome was a decrease in maternal rCBV, estimated from total-Hb, in response to a decrease in SVR during spinal anesthesia for cesarean section. From our

preliminary experiments, the effect size was estimated as 0.19 in the correlation analysis between changes in total-Hb and SVR. According to the general sample size calculation on the basis of the test for no correlation, 484 paired data needed to be included when the significant correlation coefficient between changes in total-Hb and SVR at the same timepoint was estimated with an effect size of 0.19, $\alpha = 0.01$ and a power of 0.95. Based on our previous results that hypotension appeared within 7 min after spinal injection in 70% of patients, and could be treated by injection of vasopressor agents [2], the required number of cases was estimated as 18 cases to exclude the data that would be collected after administration of vasopressor agents. In consideration of potential dropouts, this study enrolled 20 patients. The patient characteristics and clinical data are presented as means (SD) or medians (range). The time-series data for each of the 1-min intervals for HR, MAP, SpO_2, and $EtCO_2$, and for each of the 20-s intervals for CO and SVR measured by APCOs are expressed as the actual measured values, while the 20-s intervals for the NIRS measurements are expressed as their variation from baseline. The presence and absence of significant changes in the time-series data were analyzed by one-way repeated measures ANOVA or Friedman test. The relationships between the changes in total-Hb and TOI and the changes in CO and SVR at the same timepoints were evaluated by correlation analysis. For the correlation analysis, we excluded data that was measured after injection of vasopressor agents, to avoid the direct effects of vasopressor agents on NIRS and APCOs measurements. Statistical analysis was performed using JMP version 9 (SAS Institute, Cary, NC, USA). A P value of < 0.05 was considered significant.

Table 1 Demographic and clinical data

Variables	Results
Age (years)	35.1 (3.7)
Height (cm)	159.7 (5.5)
Weight (kg)	61.9 (7.6)
Gestational age (weeks)	36.9 (0.8)
Dose of bupivacaine (mg)	11.5 (0.7)
Block height, dermatome (median)	Th5 (Th2-6)
Fluids (mL)	694.5 (162.2)
Incidence of hypotension, *n* (%)	7 (41)
Pressor treatments Ephedrine, *n* (mg)	5, 9.6 (4.6)
Phenylephrine, *n* (μg)	5, 110 (54)
Incidence of adverse symptoms, *n* (%)	3 (17.6)

Data are presented as mean (standard deviation) or median (range)

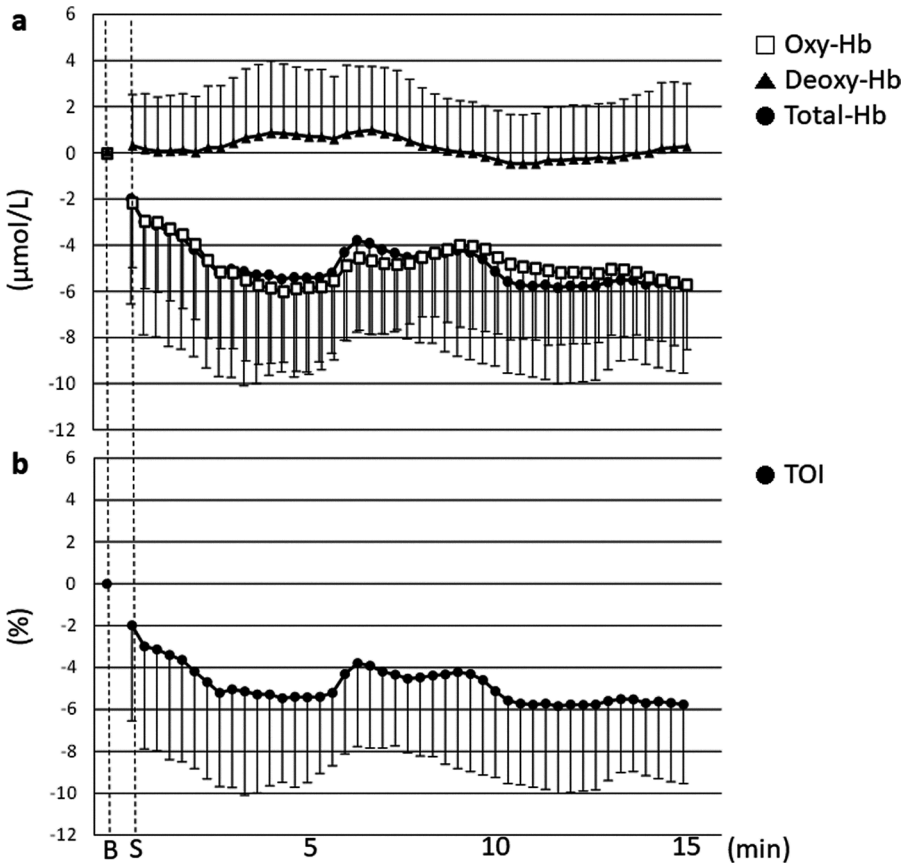

Fig. 1 Changes in near-infrared spectroscopy (NIRS) parameters after induction of spinal anesthesia. Graphs: **a** Oxy-Hb, deoxy-Hb and total-Hb, **b** TOI. Timepoints: *B* baseline, *S* immediately after induction of spinal anesthesia, *TOI* tissue oxygenation index

Results

We analyzed the data collected from 17 cases although the required sample size was 18 cases, since the required paired data for correlation analysis were appropriately collected (a total of 500 paired data) from only 17 cases. Demographic and clinical data are shown in Table 1. Hypotension and adverse symptoms were observed in 7 and 3 cases, respectively.

Changes in oxy-Hb, deoxy-Hb, total-Hb and TOI are shown in Fig. 1. There were significant decreases in oxy-Hb, total-Hb and TOI (oxy-Hb and total-Hb; $P<0.0001$, TOI; $P=0.0082$), although deoxy-Hb did not change significantly. Changes in cardiorespiratory parameters are shown in Figs. 2 and 3. MAP and SVR significantly decreased and HR significantly increased (MAP and SVR; $P<0.0001$, HR; $P=0.0002$, respectively), although CO, SpO_2, and $EtCO_2$ did not change significantly. As shown in Fig. 4, there were statistically significant positive correlations between SVR and both total-Hb and TOI (total-Hb; $r=0.1782$ $P<0.0001$, TOI; $r=0.3777$ $P<0.0001$). There was a statistically significant negative correlation between TOI and CO ($r=-0.4099$, $P<0.0001$), although there was no correlation between total-Hb and CO ($r=0.0839$, $P=0.0565$).

Discussion

The results of the present study showed that both total-Hb and TOI decreased simultaneously with the decrease in SVR after induction of spinal anesthesia. In addition, there were significant positive correlations between the changes in both total-Hb and TOI relative to the change in SVR. These results suggest that the decrease in maternal rCBV and rCBO observed after induction of spinal anesthesia for cesarean section may primarily be due to a decrease in SVR.

The present study showed that oxy-Hb, total-Hb and TOI significantly decreased from baseline in conjunction with the decrease in MAP, while deoxy-Hb and the respiratory parameters, SpO_2 and $EtCO_2$, remained unchanged. These time-course effects are consistent with our previous results [2, 6, 7], thereby suggesting once again that the decreases in rCBV and rCBO during spinal anesthesia for cesarean section are related to the mild decline in cerebral blood supply resulting from the decrease in blood pressure secondary

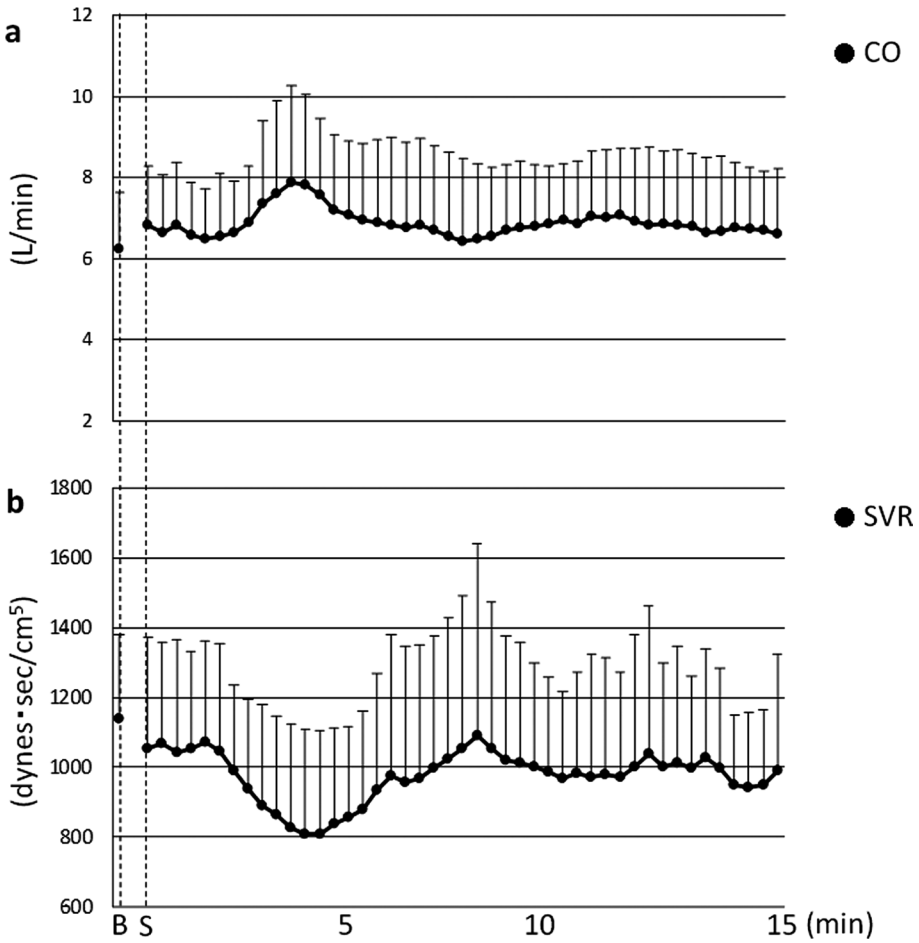

Fig. 2 Changes in cardiac output (CO) and systemic vascular resistance (SVR) after induction of spinal anesthesia. Graphs: **a** CO, **b** SVR. Timepoints: *B* baseline, *S* immediately after induction of spinal anesthesia

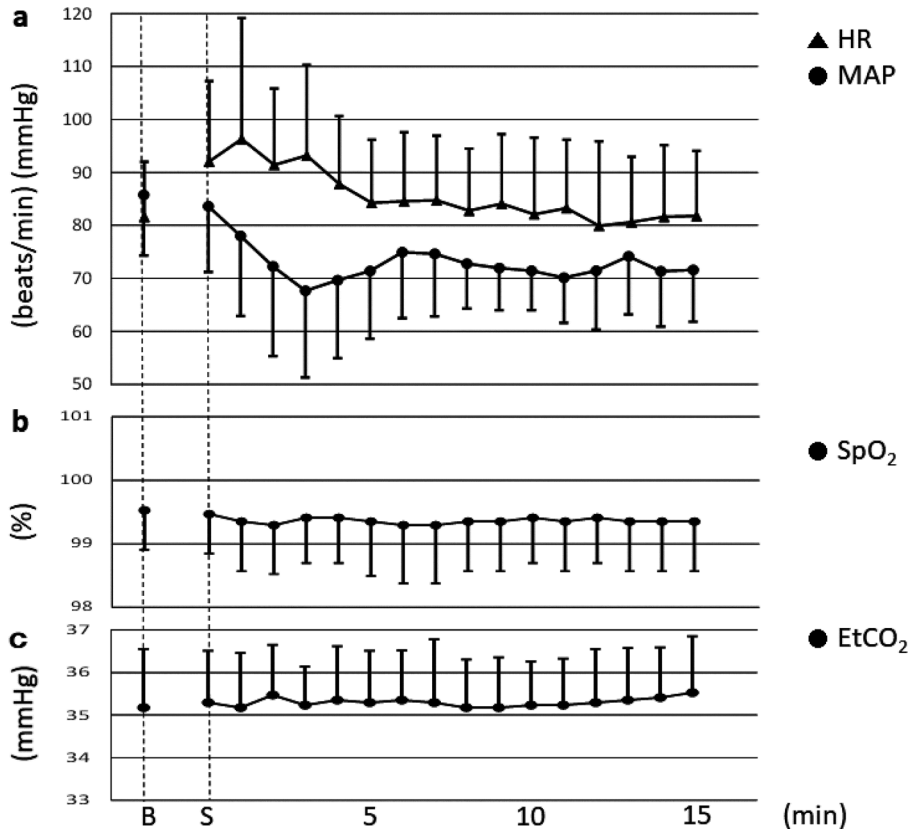

Fig. 3 Changes in heart rate (HR), mean arterial pressure (MAP), end-tidal carbon dioxide concentration ($EtCO_2$) and oxygen saturation (SpO_2) after induction of spinal anesthesia. Graphs: **a** HR and MAP, **b** SpO2, **c** $EtCO_2$. Timepoints: *B* baseline, *S* immediately after induction of spinal anesthesia

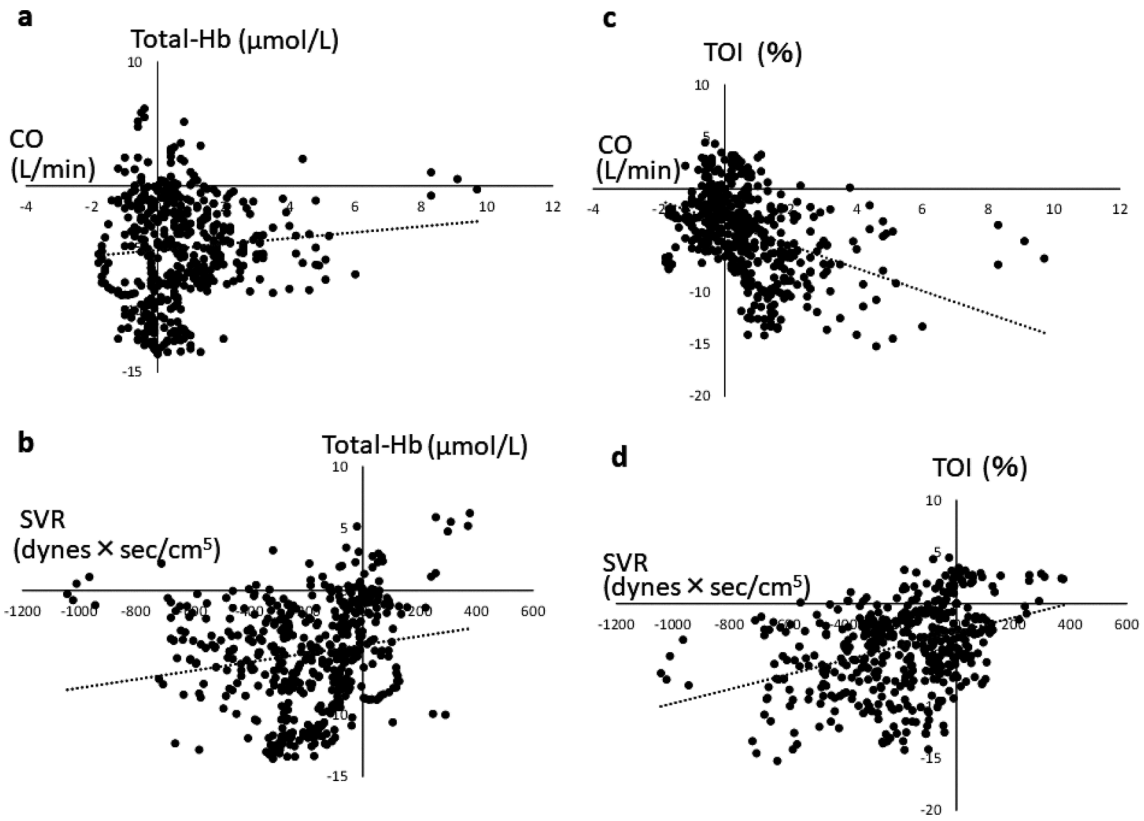

Fig. 4 Correlation between changes in CO and SVR and changes in total-Hb and TOI. Graphs: **a** CO and total-Hb, **b** SVR and total-Hb, **c** CO and TOI, **d** SVR and TOI

to spinal anesthesia. According to the accepted theory of the mechanism of autoregulation of cerebral blood flow (CBF), it is questionable whether the decrease in rCBV and rCBO in the present study depended on the decrease in MAP. However, some reports evaluating dynamic cerebral autoregulation have suggested that a transient and abrupt decrease in systemic arterial pressure within the threshold of autoregulation can decrease CBF within about 30 s [11, 12]. The present study showed that MAP decreased rapidly and continuously for several minutes after induction of spinal anesthesia for cesarean section, as is common in usual clinical settings. Based on the above, the decrease in rCBV and rCBO after spinal injection might have been caused by a delay in reactivity of autoregulation of CBF due to a mild, but rapid and continuous decrease in systemic arterial blood pressure. On the other hand, it is believed that the decrease in blood pressure during spinal anesthesia for cesarean section may depend on both the decrease in stroke volume (SV) and CO due to the decrease in venous return secondary to inferior vena cava compression by the gravid uterus [13], and the decrease in SVR due to dilatation of the vascular bed with spinal anesthesia [14]. The present study showed that MAP significantly decreased from baseline, while CO did not change significantly. In addition, the calculated SVR decreased significantly from baseline. Several studies using other non- or low-invasive hemodynamic monitoring systems, such as CircMon B202™, USCOM™ and LiDCO*plus*™, have demonstrated results that were similar to those of the present study, in which there was a decrease in SVR in conjunction with a decrease in blood pressure, even though SV and CO remained unchanged or increased slightly [8–10]. Other studies have demonstrated that low dose phenylephrine infusion, which does not lead to a significant decrease in CO with bradycardia, can effectively maintain blood pressure during spinal anesthesia for cesarean section [14, 15]. Therefore, our observation of changes in hemodynamic parameters measured by APCOs suggests once again that the decrease in blood pressure after induction of spinal anesthesia for cesarean section mainly depends on the decrease in SVR due to spinal anesthesia, and not on the decrease in CO secondary to decrease in venous return.

Taking the above discussions and the present results indicating significant positive correlations between the changes in both total-Hb and TOI relative to the change in SVR into consideration, the present study strongly suggests that the decrease in rCBV and rCBO after induction of spinal anesthesia depends on the decrease in SVR. However, the correlation coefficients between both total-Hb and SVR and TOI and SVR, especially that of the former, were low. It has been demonstrated that the Hb concentrations measured by NIRS depend on hematocrit [16], and colloid fluids reduce arterial blood oxygen content [17]. In addition, our previous study showed that the peak effect of the decrease in total-Hb appeared a few minutes later than the decrease in MAP, although the mechanism is unclear [2]. Therefore, the low correlation coefficients observed in this study might partially reflect the effect of hemodilution due to fluid loading with HES on NIRS variables, and the time difference between the onset of reduction in NIRS variables and MAP. Contrary to our expectations, the present study showed that there was a significant negative correlation between the change in TOI and the change in CO. According to the accepted theory that abrupt decrease in blood pressure leads to maintenance of CO secondary to an increase in HR through baroreflex stimulation [18], the tendency toward increase in CO with increase in HR that appeared together with the decrease in SVR might have been induced by baroreflex stimulation in response to the decrease in MAP with spinal anesthesia. Moreover, based on the fact that the decrease in CO led to a decrease in rSO_2 [19], the observed significant negative correlation between change in TOI and CO might be a spurious correlation confounded by a baroreflex.

When evaluated by NIRS, a decrease of 10–20% in cerebral oxygen saturation (ScO_2) and TOI or a decrease in oxy-Hb of 5 μmol/L accompanied by a decrease in total-Hb from baseline is suggestive of cerebral dysfunction and ischemia [20–23]. However, according to the results of the present study and our previous studies that no severe symptoms, such as those suggestive of an ischemic attack, were seen in patients despite a decrease in their oxy-Hb and TOI to below the above threshold [2, 6, 7], the decrease in rCBV and rCBO observed after induction of spinal anesthesia might be mild. However, based on our previous results that decrease in both total-Hb and TOI secondary to decrease in MAP might be indicative of an increased risk of adverse symptoms, such as nausea and vomiting [2] and that prophylactic infusion of a small dose of phenylephrine sufficiently attenuated not only the decreases in total-Hb, TOI and MAP, but also in the onset of nausea [15, 24, 25], the maintenance of rCBV and rCBO through suitable blood pressure management may have been clinically significant. In addition, the present study suggests that maintenance of SVR as a method of blood pressure management, such as by administration of phenylephrine, might be effective in suppressing the decreases in rCBV and rCBO after induction of spinal anesthesia for cesarean section.

There are several limitations to this study. First, although the data collected using NIRS predominantly reflects Hb concentrations in the frontal cortex [26], they also partially reflect Hb in extracranial tissues [27]. It is well known that NIRS is the simplest and most useful method for evaluation of cerebral circulation in the clinical setting, even though several studies have suggested that there were poor correlations between NIRS and other measurements [28, 29]. Second, in general, the value of SVR measured by the Vigileo-FloTrac™ system is calculated as SVR (dynes × s/

cm^5) = (MAP − CVP)/CO × 80 [30]. Although the SVR data obtained in this study were hypothetical values calculated as SVR (dynes × s/cm^5) = MAP/CO × 80 [31], its effects on the results would have been insignificant.

Conclusions

We examined the relationship between changes in rCBV and rCBO, and changes in CO and SVR during spinal anesthesia in women undergoing cesarean section. The present results suggest that the decreases in both rCBV and rCBO evaluated by NIRS after induction of spinal anesthesia depend mainly on decreases in SVR.

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