Original Article

The predictive ability of non-invasive haemodynamic parameters for hypotension during caesarean section: a prospective observational study*

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Summary

Spinal anaesthesia for caesarean section induces hypotension, which may cause severe adverse effects. Our goal was to determine whether hypotension could be predicted by pulse oximetry parameters, such as the perfusion index and pleth variability index, heart rate, ratio of low-frequency to high-frequency components of heart rate variability, and entropy of heart rate variability, measured before the induction of anaesthesia. The predictive value of these parameters for detecting hypotension was assessed using logistic regression and the grey zone approach in 81 parturients. Logistic regression revealed heart rate to be the only independent predictor (OR 1.06; 95% CI 1.01–1.13; p = 0.032). The grey zone for heart rate was in the range of 71–89 bpm, and 60.5% of parturients were in the grey zone. Pre-anaesthetic heart rate, but not other parameters derived from pulse oximetry or heart rate variability, may be a prognostic factor for hypotension associated with spinal anaesthesia.

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Introduction

Caesarean section is commonly performed under spinal anaesthesia, because it has many advantages over general anaesthesia. However, spinal anaesthesia can result in hypotension, which may cause severe adverse effects in mothers, such as nausea, vomiting and dizziness, and may cause umbilical arterial acidosis in infants. An ability to identify those who would suffer from hypotension following spinal anaesthesia would give clinicians an opportunity to take preventative measures.

Baseline peripheral vasomotor tone [1], volume status [2] and sympathetic activity [3] are known to affect the degree of hypotension after spinal anaesthesia in parturients undergoing caesarean section. We therefore hypothesised that the perfusion index (PI), pleth variability index (PVI), heart rate, and parameters of heart rate variability (HRV) may predict hypotension.

The PI measured by pulse oximetry reflects vasomotor tone, and is calculated as the ratio of the pulsating arterial flow to non-pulsating blood in the peripheral tissues [4]. A lower PI indicates greater peripheral vasomotor tone. The PVI is an automatic measure of the dynamic change in the PI, caused

mainly by respiration, and may be used as an index of the volume status. Higher PVI values reflect larger respiratory fluctuation of the PI values, and may indicate greater fluid responsiveness.

Heart rate and HRV reflect sympathetic activity. Spectral analysis included in a linear analysis of HRV is used to estimate autonomic nervous activity, by calculating the ratio of the low-frequency (LF) component (indicator of parasympathetic and sympathetic nervous activity) to the high-frequency (HF) component (indicator of parasympathetic nervous activity) (LF-to-HF ratio). On the other hand, entropy, which is calculated by a non-linear analysis of HRV, provides insight into the overall structure of the heart rate regulatory system [5].

The aim of our study was to investigate whether the PI, PVI, heart rate, LF-to-HF ratio, and entropy measured before the induction of spinal anaesthesia could predict hypotension during caesarean section.

Methods

We conducted this prospective, observational study following approval by our institutional ethical committee (Yokohama City University Hospital, Yokohama, Japan). Written, informed consent was obtained from each patient before inclusion. We enrolled pregnant women who were to undergo an elective caesarean section at the Yokohama City University Hospital, Yokohama, Japan, between November 2011 and September 2013. The exclusion criteria included a gestational age of < 36 weeks of pregnancy, pregnancy-induced hypertension, diabetes, cardiovascular diseases, arrhythmia, pre-eclampsia, total placenta praevia, and BMI above 36 $kg.m^{-2}$. Parturients who could not maintain a supine position, and those who had any clinical fetal complications, were also not studied.

We performed non-invasive blood pressure measurements, electrocardiography and pulse oximetry on subjects on their arrival in the operating room. We placed the cuff of an automated non-invasive blood pressure device (Life scope®, DM-910P; Nihon Koden, Tokyo, Japan) on the right arm, and attached the pulse oximeter probe (Masimo Radical 7; Masimo Corp., Irvine, CA, USA) to the left index finger. The Radical 7 measures the PI, which is the ratio of the pulsatile infrared signal to the non-pulsatile infrared signal, expressed as a percentage. The PVI is an automatic measure of the dynamic change in the PI throughout the respiratory cycle, and is calculated using the following formula: $PVI = ([PI_{max} - PI_{min}]/PI_{max}) \times 100$.

Following a 2-min resting period, we measured pre-anaesthetic PI, PVI, heart rate, LF-to-HF ratio and entropy for 3 min in a supine position. We recorded the parameters at 10-s intervals, and their average or median values were defined as their respective pre-anaesthetic values.

We digitised an electrocardiogram signal obtained at 1000 Hz from an anaesthesia monitor, transferred it to a personal computer (FMV-BIBLIO MG/D75; Fujitsu, Tokyo, Japan), and determined the RR intervals. An on-line analysis of HRV was performed using the MemCalc method (Memcalc/Tarawa; Suwa Trust, Tokyo, Japan), a combination of the maximum entropy method for the spectral analysis and non-linear least squares method for fitting analysis. It provides reliable analyses of HRV over a minimum interval of 30 s. While it recognises an abnormal RR interval of premature beats or artefacts, including noise, and removes them automatically, the MemCalc method does not distort the power calculation. The powers of the RR intervals (ms^2) with the LF component (0.04–0.15 Hz) and HF component (0.20–0.40 Hz) bands were calculated. The LF component is affected by both cardiac sympathetic and parasympathetic activity, and the HF component originates from cardiac parasympathetic activity. Thus, the LF-to-HF ratio reflects the dominance of cardiac sympathetic activity. Therefore, we assessed the LF-to-HF ratio in RR interval variability.

In addition, in the MemCalc program, entropy was calculated from pulse time series of eight RR intervals. This index provides information about the entropy of the RR intervals as a non-linear index of HRV, and addresses system randomness, irregularity and unpredictability. Thus, entropy is expressed as a percentage from zero (pulse series of the regular interval, no variability) to 100 (maximal randomness such as noise) [6]. A decrease in entropy is considered to represent the decreased activity of the heart rate regulatory system. An increase and decrease in entropy are often associated with greater parasympathetic and sympathetic activity, respectively [5–8].

Combined spinal-epidural anaesthesia was performed according to the following protocol. An epidural catheter was placed at the T12-L1 interspace (this interspace was chosen to minimise the postoperative incisional pain, in keeping with common Japanese practice), and spinal anaesthesia was induced at the L3-4 or L4-5 interspace with 10 mg hyperbaric bupivacaine 0.5% and 10 μg fentanyl, with the patient in a right lateral position. After spinal injection, the parturient was returned to the supine position with a left lateral tilt of about 10°, to facilitate left uterine displacement. Then, oxygen 4 $l.min^{-1}$ was supplied via a facemask. Surgical incision was allowed when a block level to at least the T6 dermatome was obtained to both cold and pinprick. If the block to the T6 level was not achieved within 10 min following spinal injection, the parturients were not included in the study, and the local anaesthetic was administered through the epidural catheter to obtain adequate anaesthesia for the surgery.

A rapid infusion of hydroxyethyl starch 6% (Hespander®, Fresenius Kabi Japan, Tokyo, Japan) was started immediately after the spinal injection and continued until delivery. No prophylactic ephedrine was administered. Non-invasive blood pressure was measured every minute between the spinal injection and delivery. Hypotension was defined as a systolic blood pressure below 80 mmHg after spinal anaesthesia, and was treated immediately with intravenous administration of 8 mg ephedrine. For safety reasons, rescue ephedrine was given if the patient demonstrated clinical signs of cerebral hypoperfusion, such as dizziness, nausea, or vomiting, even if systolic blood pressure was above 80 mmHg. These patients were classified as the hypotensive group. The reasons behind these choices are elaborated on below. Bradycardia was defined as a heart rate below 50 bpm, and was treated with 0.5 mg atropine. The study ended with delivery of the baby. Umbilical arterial pH and the Apgar scores (after 1 and 5 min) were recorded after delivery.

We used the unpaired t-test, Mann–Whitney U-test and Fisher's exact test, as appropriate, to compare patients' characteristics, neonatal outcomes and pre-anaesthetic values of each parameter, between parturients who developed hypotension and those who did not. Logistic regression was used to examine associations between hypotension and age, height, weight, abdominal circumference, PI, PVI, heart rate, LF-to-HF ratio and entropy. All these parameters were checked for multicollinearity. If there was a correlation between any pair of parameters, we excluded one of them from the logistic regression model. We used a forward stepwise selection procedure to develop the final regression model, selecting the model with the lowest value of the Akaike's information criterion at each step [9].

We examined the ability of the final model to predict hypotension, generating receiver operating characteristic (ROC) curves with the bootstrap method (resampling time, 2000), and calculating the area under the curve. Youden's index (J = sensitivity + specificity − 1) [10], defining the value of the studied outcome maximising both sensitivity and specificity, was also calculated.

In addition, we used the grey zone method to determine the optimal pre-anaesthetic value of the final model. The purpose of this analysis was to minimise the risks of misclassification, by showing the range of values where a prediction of hypotension was inconclusive [11]. First, the points where sensitivity and specificity each became 90% (diagnostic tolerance of 10%) were calculated. The grey zone was determined as the range between the two points, and expressed as low limit–high limit.

Data normality was tested by the Kolmogorov–Smirnov test. All parametric data were expressed as mean (SD) and non-continuous data as median [IQR (range)]. Values with $p < 0.05$ were considered statistically significant. All statistical analyses were performed with the R statistical software package version 2.13.0 (R foundation for Statistical Computing, Vienna, Austria).

Results

We enrolled 95 patients, and 81 completed the study. Fourteen patients were not studied because of deviation from the study protocol (n = 5) and failure to achieve the sensory block level of T6 (n = 9). Hypotension occurred in 51 of 81 patients (63%). Five of the hypotensive patients received ephedrine before the systolic blood pressure fell below 80 mmHg, because

of clinical signs of cerebral hypoperfusion. Of the 81 patients, four received atropine. In one patient, atropine was given after the systolic blood pressure fell below 80 mmHg, and this patient was classified in the hypotensive group. The remaining three patients never experienced a systolic blood pressure below 80 mmHg, and were classified in the normotensive group. In one of those patients, atropine was given 10 min after the nadir of the blood pressure occurred. In the remaining two patients, it was given when the systolic blood pressure was relatively stable above 80 mmHg.

The week of pregnancy, height and weight were similar in those subjects who developed hypotension and those who did not (Table 1). There were no significant differences in the level of the sensory block, blood loss, or the rate of infusion of hydroxyethyl starch between the groups (Table 1). The status of the neonates, as determined by the Apgar score and pH of the umbilical artery, was similar between the groups (Table 2).

Table 3 demonstrates the pre-anaesthetic haemodynamic parameters in patients who became hypotensive during caesarean section, and those who did not. The pre-anaesthetic heart rate was significantly higher in the hypotensive group ($p = 0.008$). On the other hand, the PVI and PI were not different between the groups ($p = 0.66$ and 0.86, respectively). There was a tendency to a higher LF-to-HF ratio and lower entropy for those who developed hypotension ($p = 0.13$ and 0.11, respectively), but the difference did not reach statistical significance.

Table 4 demonstrates the results of the logistic regression analysis. Abdominal circumference was excluded, because multicollinearity was proved between weight and abdominal circumference. Logistic regression analysis identified heart rate as the only independent factor to predict hypotension (OR 1.06 (95% CI 1.01–1.13), $p = 0.032$; Table 4). The final logistic regression model included heart rate (OR 1.06 (95% CI 1.01–1.11), $p = 0.012$), but none of the other parameters. The area under the curve of the ROC curve was 0.686 (95% CI 0.558–0.803; Fig. 1). The best cut-off point using Youden's index of a pre-anaesthetic heart rate was 73, with a sensitivity of 86.3% (95% CI 76.5–94.1%), and specificity of 50% (95% CI 33.3–66.7%).

The grey zone analysis revealed that the lower and higher limits of the grey zone were 71 and 89 bpm, respectively. The number of parturients in the grey zone was 49 (61%).

Discussion

We have demonstrated that a higher pre-anaesthetic heart rate is associated with hypotension following spinal anaesthesia for caesarean section, while more modern and sophisticated parameters such as PI, PVI, LF-to-HF ratio, and entropy, did not remain in the final logistic regression model, and were not predictive for hypotension.

A high heart rate generally reflects enhanced activity of the sympathetic nervous system. Therefore, parturients with higher pre-anaesthetic heart rates were

Table 1 Characteristics of parturients who developed hypotension and those who did not. Values are median (IQR [range]), mean (SD) or number (proportion).

	Hypotension (n = 51)	Normotension (n = 30)	p value
Age; years	35 (32–37 [25–43])	34 (31–37 [23–42])	0.53
Pregnancy; weeks	38 (38–38 [37–38])	38 (37–38 [36–38])	0.31
Abdominal circumference; cm	94 (5)	94 (7)	0.53
Height; cm	159 (6)	160 (6)	0.86
Weight; kg	64 (8)	62 (9)	0.46
Sensory block level	T3 (T2–T4 [C5–T5])	T3 (T1–T6 [C6–T6])	0.28
Blood loss; ml	1105 (491)	1155 (578)	0.68
Infusion rate; $ml.min^{-1}$	17 (4)	19 (6)	0.12
Puncture site			
L3-4	49 (61%)	29 (36%)	1
L4-5	2 (2%)	1 (1%)	

Table 2 Outcomes of neonate in parturients who developed hypotension and those who did not. Values are median (IQR [range]) or mean (SD).

	Hypotension (n = 51)	Normotension (n = 30)	p value
Apgar score			
1 min	8 (8–9 [6–9])	8 (8–9 [5–9])	0.17
5 min	9 (9–9 [8–10])	9 (9–9 [7–10])	0.97
Umbilical arterial blood			
pH	7.26 (0.08)	7.29 (0.08)	0.13
PCO_2; mmHg	51 (12)	48 (12)	0.36
PO_2; mmHg	22 (9)	22 (10)	0.99
Newborn weight; g	2993 (290)	2785 (305)	0.003
Newborn height; cm	48 (2.4)	48 (2.1)	0.31

Table 3 Pre-anaesthetic value of pulse oximetry and electrocardiographic parameters in parturients who developed hypotension and those who did not. Values are mean (SD) or median (IQR [range]).

	Hypotension (n = 51)	Normotension (n = 30)	p value	Differences in means/medians (95% CI)
Perfusion index; %	6.1 (3.3)	5.9 (2.2)	0.86	0.2 (−1.2 to 1.4)
Pleth variability index; %	18.4 (6.6)	17.8 (4.9)	0.66	0.6 (−2.2 to 3.5)
Heart rate; bpm	84 (10)	77 (13)	0.008	7 (2–12)
Heart rate variability				
LF/HF	2.5 (1.6–3.5 [0.2–18])	2.0 (1.2–2.9 [0.3–9.1])	0.13	0.5 (−0.3 to 1.1)
Entropy	47 (6.5)	50 (10)	0.11	−3 (−7.0 to 0.4)

CI, confidence interval; LF/HF, low frequency and high frequency rate of heart rate variability.

presumably more dependent on sympathetic tone to maintain their blood pressure. Because spinal anaesthesia causes hypotension by blocking the sympathetic innervation to the cardiovascular system, it is reasonable, and perhaps unsurprising, that spinal anaesthesia produced a greater decrease in blood pressure in those parturients with higher heart rates in our study.

Table 4 Results of logistic regression analysis to predict maternal hypotension during elective caesarean section.

	OR	95% CI	p value
Age	1.06	0.94–1.20	0.32
Weight	1.03	0.96–1.10	0.49
Height	0.96	0.87–1.05	0.35
Perfusion index	0.97	0.81–1.17	0.78
Pleth variability index	1.01	0.93–1.11	0.76
Heart rate	1.06	1.01–1.13	0.032
LF/HF	0.96	0.80–1.14	0.60
Entropy	0.98	0.91–1.06	0.63

LF/HF, low frequency and high frequency rate of heart rate variability.

Previous studies, however, have shown conflicting results. Some demonstrated a significant correlation between the baseline maternal heart rate and subsequent ephedrine requirements [12], while others showed no relationship between hypotension and baseline heart rate [1, 13]. This discrepancy appears consistent with a relatively weak correlation between pre-anaesthetic heart rate and hypotension, as suggested by the area under the curve of 0.686 in the ROC curve in our study, and relatively low OR.

We also demonstrated that the cut-off point of pre-anaesthetic heart rate for predicting hypotension was 73 bpm, with the sensitivity and specificity of 86% and 50%, respectively. This means that, among parturients whose pre-anaesthetic heart rate was > 73 bpm, hypotension occurred in 44 (i.e. 86% of 51 parturients who developed hypotension) and did not occur in 15 (i.e. 50% of 30 parturients who did not develop hypotension). Therefore, the risk of hypotension in this group was 75% (=44/(44 + 15)). On the other hand, among those whose pre-anaesthetic heart rate was less than 73 bpm, hypotension occurred in seven, and did

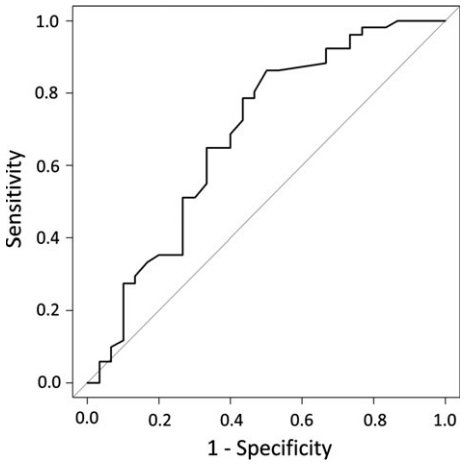

Figure 1 Area under the receiving operator characteristic curve for heart rate. Area under the curve: 0.686, 95% CI 0.558–0.803 (2000 stratified bootstrap replicates).

not occur in 15 parturients, respectively. This yields a risk of hypotension of 32% (=7/(7 + 15)) in this group. It is unclear how useful the cut-off point that differentiates between a risk of 75% and a risk of 32% is.

The grey zone analysis revealed that 60% of our patients were included in the grey zone of the heart rate between 71 and 89 bpm. The value of this grey zone analysis lies in the fact that we were successful in identifying with high certainty the remaining 40% patients who would or would not develop hypotension during a caesarean section. Such information may be more clinically relevant than a simple cut-off value, because prophylactic measures against hypotension during a caesarean section, such as administering vasopressors, may cause complications (e.g. reactive hypertension, bradycardia or tachycardia in the mothers, and a decrease in maternal cardiac output) [14–16]. Further investigation is required to clarify whether baseline heart rate helps anaesthetists to use these preventive measures more safely.

Generally, the frequency and magnitude of hypotension produced by spinal anaesthesia is dependent on the intravascular volume. Therefore, we predicted that the PVI might predict hypotension during a caesarean section under spinal anaesthesia. However, our results failed to demonstrate this. The reason for this is unclear, and our study was not designed to elucidate it. We speculate that PVI may not be a reliable index of intravascular volume in spontaneously breathing parturients, although its value during mechanical ventilation in the general population has been more robustly demonstrated. Even so, a threshold PVI value above 19% in healthy volunteers was only a weak predictor of the response to the passive leg raise test (sensitivity, 82%; specificity, 57%; area under the curve of the ROC, 0.734 $\pm$ 0.101) [17].

Recently, Toyama et al. [1] have reported that pre-anaesthetic PI can predict hypotension during caesarean section, but our results suggest otherwise. The reasons for this discrepancy might be as follows. Firstly, there were several methodological differences between the studies. In our study, hypotension was defined as a systolic blood pressure below 80 mmHg, and rapid infusion of colloids was started just after spinal anaesthesia as a co-load of colloid. In the other study, hypotension was defined as a decrease of > 25% from baseline systolic blood pressure, and infusion of 500 ml colloid was started before spinal anaesthesia as a preload. It is unclear whether the pre-anaesthetic PI was measured before or after the preload. Secondly, there were differences in the calculation of the representative values of pre-anaesthetic PI. In our study, the PI was recorded at 10-s intervals for 3 min, and the average value of those data was defined as the pre-anaesthetic PI. In the other study, we found no details of how the baseline PI was determined. Because the PI fluctuates every few seconds, the way the representative PI is determined may affect the interpretation of the result. Finally, the PI is commonly affected by factors such as movement, temperature, psychological stress and anxiety, which can induce sympathetic activation. It is difficult to control for these factors in all awake patients. Further examination is necessary to elucidate whether the PI is a truly reliable index.

Heart rate variability might be used to predict haemodynamic changes associated with anaesthesia. A previous study involving 19 parturients undergoing caesarean section reported that hypotension after spinal anaesthesia was related to a high pre-anaesthetic LF-to-HF ratio, which indicates high sympathetic nervous activity [3]. Recently, the usefulness of the MemCalc method has been reported in some anaesthesia-related studies [5–7, 18]. Lower baseline entropy in parturients might represent intrinsic circulatory

vulnerability to spinal anaesthesia. However, we were not able to show that either LF-to-HF ratio or entropy was predictive of hypotension. This may be because these parameters are easily affected by maternal psychological stress, which differs between individuals.

Our study has several limitations. First, the movement of patients, and various stimuli that cause sympathetic vasoconstriction such as mental stress, anxiety, and cold temperature, might decrease the accuracy of the PI and PVI. To minimise measurement errors, the patients in our study were listening to relaxing classical music, the temperature of the operating room was maintained at 25 °C, and they were asked to remain calm. However, it is unlikely that these conditions were uniform among all the patients, which may represent a limitation of studies in awake patients.

Secondly, the definition of hypotension in this study as a systolic blood pressure of < 80 mmHg may be considered inadequate. However, we decided to use this level based on a previous report [3], despite other authors' suggesting thresholds based on percentage change from baseline. If hypotension was defined as a decrease in systolic blood pressure of 20% from baseline in our study, hypotension occurred in 67 of 81 subjects. This included two parturients who received ephedrine before their blood pressure fell by more than 20% from baseline. The pre-anaesthetic parameters such as PI, PVI, heart rate, LF/HF, and entropy were similar between those who developed hypotension using this definition, and those who didn't. The validity of this subsequent analysis may be questioned, however, because of the marked imbalance in the number of parturients in the two groups (67 vs 14). On the other hand, if hypotension was defined as a decrease in systolic blood pressure of 30% from baseline, hypotension occurred in 50 of 81 subjects, including eight parturients who received ephedrine before the systolic blood pressure decreased by 30% from baseline. Again, heart rate was the only parameter that was different between the two groups. We also believe that our definition of hypotension was safe for low-risk parturients undergoing an elective caesarean section. In our study, the mean umbilical arterial pH was above 7.2 in both hypotensive and normotensive groups, and no newborn had a pH < 7.0, which is considered to be a better threshold value for safety [19]. Furthermore, for safety reasons, we administered rescue ephedrine in patients with clinical signs potentially suggestive of cerebral hypoperfusion.

Thirdly, our protocol required the use of atropine for bradycardia (heart rate below 50 bpm). Atropine could have prevented hypotension by increasing the heart rate, and thereby increasing the cardiac output. Two patients in our study received atropine when the blood pressure was relatively stable at above 80 mmHg. We classified those patients as normotensive, but we cannot exclude the possibility that their blood pressure might have dropped to < 80 mmHg if atropine had not been given. However, repeated analyses of the data after excluding those two patients did not affect the result, showing that heart rate was the only predictor of hypotension.

Finally, our sample size of 81 parturients (95 recruited, with 14 subsequently excluded) was small, and lack of statistical significance for variables other than heart rate may have been due to lack of power. However, the p values in the logistic regression analysis are relatively large, except for that for heart rate, suggesting that impractically large numbers of subjects would need to be studied to detect a difference, if any.

In conclusion, we have demonstrated that pre-anaesthetic heart rate is a predictor of hypotension after spinal anaesthesia for caesarean section in healthy women. In particular, we demonstrated that heart rates of < 71 bpm, and more than 89 bpm, are clinically useful prognostic values to help predict the development of hypotension, while those in the range between have relatively weak prognostic value. Unlike some previous studies, we showed that pre-anaesthetic PVI, PI, LF-to-HF ratio and entropy of HRV are not useful indices to predict hypotension in this patient group.

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Competing interests

No external funding and no competing interests declared.

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