Shock Index Values During the Peripartum Period in Patients Under Neuraxial Labour Analgesia: a Multicentre Prospective Cohort Study

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Abstract

Objective: We aimed to assess the association between intrapartum neuraxial labour analgesia (NLA) and shock index values during the peripartum period. Design: A multicentre prospective cohort study. Setting: Two reference centres in Colombia. Population: Obstetric patients in labour with term gestations were divided according to whether they underwent NLA between 2017 and July 2018. Methods: We collected maternal blood pressure and heart rate within the first and second stages of labour and every 30 minutes up to two hours postpartum. We assessed the association between intrapartum NLA and shock index values in a multivariable longitudinal mixed-effect model, adjusting for covariates. Main outcome measures: Shock index changes over time during labour and postpartum periods. Results: We included 522 patients, 228 (43.7%) with NLA and 294 (56.3%) without NLA. Except in the first stage of labour [0.68 (IQR, 0.63-0.74) vs 0.73 (IQR, 0.64-0.82); p=0.07], the shock index values were significantly higher in patients with NLA during the second stage of labour and postpartum (all p values <0.001). In the longitudinal mixed-effect model analysis, shock index values were higher in the NLA group. After adjusting the multilevel model by age, nulliparity, and cervical dilation, the mean shock index without NLA across the measurements was 0.69, while in NLA was 0.76 (mean difference of 0.067). Conclusions: In patients receiving NLA, the shock index values during labour differ from those during the postpartum period. Thus, under these conditions, the shock index should be interpreted differently. Keywords: Shock Index; Neuraxial Labour Analgesia; Postpartum Haemorrhage.

INTRODUCTION

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality, with an estimated 34,000 deaths occurring worldwide in 2017.[1] There are profound disparities in maternal deaths due to PPH, with nearly 90% of all cases occurring in low middle-income countries.[1] The conventional definition of PPH is a blood loss of [?]500 ml after a vaginal delivery or [?]1,000 ml in a caesarean section.[2] Despite this, current blood loss estimation methods are inaccurate, leading to underestimating PPH incidence.[3] Because of this, recent initiatives have suggested that the combination of hemodynamic variables with blood loss estimation might improve the early identification and definition of PPH.[4]

The current literature proposes new indices, such as the shock index (SI = the ratio of heart rate (HR) to systolic blood pressure (SBP)], as a valuable clinical sign of haemodynamic instability in the general population. This parameter also shows a strong ability to predict adverse outcomes in trauma,[5] sepsis[6]and hypovolemic shock.[7] Moreover, cumulative evidence emphasises its value as a prognostic factor in PPH cases,

anticipating the need for massive transfusion, admission to an intensive care unit (ICU), and development of severe morbidity.[8,9] In the general population, SI values range from 0.5 to 0.7.[7]In pregnant women, this value varies from 0.7 to 0.9, and a cut-off value [?] 0.9 is considered a threshold for urgent care.[13–16.] However, these studies did not consider confounding factors such as pain, obstetric analgesia, or maternal anxiety that might induce haemodynamic changes, leading to changes in SI values.[13–15]

The use of neuraxial labour analgesia (NLA) is becoming popular in high- and middle-income countries[21,22,] owing to its high reliability, superior pain relief, high patient satisfaction, and low incidence of complications.[16,18] The use of NLA has been shown to result in changes in blood pressure and HR.[19,20] We hypothesised that SI values in patients under NLA during labour and the postpartum period would be different from the SI values of those who did not receive NLA.[13,20–22] Thus, we aimed to compare the changes in SI values during the active phase of labour up to the first two hours postpartum in patients with or without intrapartum NLA.

METHODS

Ethics

Before recruitment, ethical approval was provided by the Institutional Review Board of the Universidad de Cartagena (Ethical Committee No. 022/2017), Cartagena, Colombia (Chairperson Prof. A. Olivera) on 16 May 2017. Additionally, all patients signed an informed consent form.

Study design

This was a prospective cohort study that included patients with singleton gestations with spontaneous onset of labour admitted to two obstetric centres in Colombia (Clínica Maternidad Rafael Calvo (CMRC) in Cartagena and Clínica Universitaria Bolivariana (CUB) in Medellín) between December 2017 and July 2018.

Patients

We included women with singleton gestations at term ($>$ 37 weeks) between 18 and 45 years of age admitted due to spontaneous labour onset. Exclusion criteria were 1) previous or current comorbidities (preeclampsia, gestational diabetes, recurrent urinary tract infections, or an episode of vaginal bleeding during the second half of pregnancy); 2) maternal pyrexia at admission, defined as a temperature of 38.0 °C once or 37.5 °C on two occasions two hours apart. 3) tobacco exposure in the previous 24 hours; 4) haemoglobin level $<$9 g/dL; 5) contraindications or refusal of neuraxial blockade; and 6) current use of medications with known influence on the cardiovascular system. Additionally, patients with failed neuraxial blockade or replacement of the epidural catheter due to inadequate pain control were not included in the final analysis. Patients were classified according to whether they were under NLA during labour.

Analgesia protocol

In CMRC, obstetric analgesia is not considered a pain management standard during labour and is not used in any patient. In contrast, CUB incorporates obstetric analgesia as the standard of care for all patients; therefore, all participants with NLA were limited to CUB. Maternal vital signs and foetal tracing were monitored during analgesia (Philips IntelliVue MP20). All patients were evaluated by a consultant obstetrician every 3 h. At the patient's request, a cervical examination was performed at the time of analgesia. We defined the active phase of the first stage of labour as cervical dilation [?] 4 cm and cervical effacement [?] 80%. The neuraxial blockade technique (epidural, spinal, or combined spinal-epidural) was selected according to the stage of labour. In patients with cervical dilation below 5 cm, the epidural technique was the preferred technique, while in those $>$ 5 cm accompanied by moderate to severe pain, combined spinal-epidural analgesia was selected. The visual analogue scale for pain (VAS-P) was used for pain assessment. The entire protocol is described in

Appendix S1.

Data collection

Two qualified nurses obtained all data. Clinical characteristics included maternal age, height, weight, body mass index (BMI), parity, gestational age (GA), and haemoglobin concentration. The SI was defined as the ratio of HR to SBP.[23] to measure HR and SBP, which was measured using a digital calibrated sphygmomanometer (Omron M6 Comfort, OMRON Healthcare, Kyoto, Japan). For all cases, at least seven measures of the SI were obtained: 1) at the active phase of the first stage of labour, 2) during the second stage of labour, 3) within 15 min postpartum, and 3) every 30 minutes until two hours postpartum (four measures). All SI values were masked by the treating clinicians and used only for research purposes. Based on the World Health Organization criteria, maternal anaemia was defined as less than or equal to 11 g/L.[24] The presence of PPH as registered on the clinical charts was also recorded. All patients were followed up until their discharge.

Statistical analysis

Categorical variables are described as percentages, and continuous variables are expressed as the means or medians with dispersion measures. The Kruskal-Wallis, and Pearson chi-square tests were used to perform uni and multivariate comparisons of quantitative and qualitative variables, respectively. A longitudinal analysis with repeated measures of SI was performed using a linear mixed-effects model, where we tested the main association of NLA on the change in SI during labour and postpartum, comparing the association of interventions on SI across labour and postpartum. The analyses were fitted using an unstructured random slope and intercept, using the R package 'lme4'. We chose this structure following the recommendation of using it on outcomes with a ratio scale, such as SI.

We tested whether the changing trend was different between the NLA and non-NLA groups. The primary outcome was the SI values for a patient over time during labour and postpartum periods. Therefore, the primary hypothesis of the study can be formally stated as a test of whether there is a time x intervention interaction. We tested the interaction by fitting a multilevel model with SI as the dependent variable at each time and with the time period, analgesia status (NLA or non-NLA), and the NLA-time period interaction as fixed effects. We assumed that the time between each measure (antepartum and postpartum) was equal for statistical analysis.

The association between NLA status and SI was adjusted in the linear mixed-effects model by maternal age (older than 35 years), haemoglobin level, cervical dilation, and nulliparity. We categorised continuous variables and entered them as terciles in the multilevel model to account for the nonlinearity of the relationship with SI. We also fitted the models for each component of the SI (HR and SBP). We excluded confounders with p values >0.50 in the fitted model with all covariates and excluded these nonsignificant covariates from further analysis. The associations for all other assessments were deemed significant if the p-value was <0.05. We reported the β-coefficients of each fitted model and estimated the 95% confidence interval (95% CI). Finally, we performed sensitivity analyses to measure changes in the β-coefficients and significance by type of NLA, including only the most frequently used type of analgesia worldwide (i.e., epidural analgesia).

Sample size estimation

Response variables

For repeated measures analysis, the primary response variable of interest was the SI value. The SI is a continuous variable that ranges from 0.7 to 0.9, with 0.7 meaning the minimum expected range and 0.9 meaning the maximum normal limit.[13–16].SI was assessed immediately upon admission to the labour room in the active stage of labour (time 0), at the second stage of labour (time 1), and every 30 minutes until two hours postpartum (30-60-90-120 minutes, time 2 to 5).

Predictor variables

The primary predictor of interest was NLA. Patients were selected for either the NLA or non-NLA group based on the clinic (CUB or CMRC). Those in the NLA group (CUB) received the analgesia protocol according to the physician's discretion. Patients without NLA (CMRC) had the same protocol, except for the inclusion of any analgesia protocol.

Variance and correlation patterns

We estimated that the SI measured a clinically significant mean difference change of 0.06 as clinically significant. The variance of the difference between time 0 and time 1 was estimated to be 0.0097 based on a previous study conducted by Borovac and colleagues.[25] We used this variance of difference as an estimate for the variances of the SI measures within subjects. Based on the previous data, with a specified minimal change in SI, a mean difference of 0.06 between the SI measures was considered clinically significant. A sample size of 252 patients per group, or a total of 504 patients, would give a power of at least 0.8 for testing the hypothesis.[30.]

The sample size estimation for the longitudinal analysis was performed using the *General Linear Mixed Model Power and Sample Size*software GLIMMPSE (URL: http://glimmpse.samplesizeshop.org/). All other analyses were performed using the R statistical software package (version 4.0.3). This report was written following the Enhancing the QUality and Transparency of Health Research (EQUATOR) STROBE guidelines.

RESULTS

Patient characteristics

A total of 682 patients were enrolled in this study. One hundred sixty patients (138 with hypertensive disorders, eight with caesarean deliveries, seven with anaemia, six with preterm deliveries, and one with pyrexia) were excluded **(Figure S1).** A total of 522 patients were included in the final analysis: 228 (43.7%) with NLA and 294 (56.3%) without NLA. Patients with NLA had a median age of 25.5 years [IQR, 20-28], while patients without NLA had a median age of 23 years (IQR, 21-30); p<0.001). Table 1 displays the clinical characteristics, interventions, and outcomes of each group. Patients with NLA had a significantly greater median age, greater frequency of nulliparity, higher haemoglobin, and less cervical dilation. Most NLA procedures were performed as an epidural technique (96.1%). There were no other differences in the other variables between the groups. In**Table S1** , we describe the missing data for each variable.

In the NLA group, 31 (13.6%) patients required the administration of one or more uterotonics. Eighty-seven percent (n =27) required methylergonovine, 22.6% (n =7) required carbetocin, and 26.2% (n =5) required misoprostol. A total of 183 patients (80.6%) in the NLA group received more than two boluses of analgesia. The presence of PPH was similar between patients with and without NLA.

Association between NLA and SI values across repeated measurements

The crude trends and 95% CI of the multilevel regression model across repeated measures for SI, HR, and SBP are shown in **Figure 1(a-c)** . The mean raw values of SI, HR, and SBP are shown in**Figures 1a, 1b, and 1c,** respectively (as dots).

In our sample, the SI was higher in women with NLA, and this difference increased as labour progressed. This association can also be seen in the raw mean SI values (**Table 2**). At the start of the first stage of labour, the mean difference in SI between the NLA and non-NLA groups was 0.04, and this raw mean difference increased to 0.10 after 120 minutes of the postpartum period.

These differing trends in the SI continued after adjustments in the multilevel model (**Table S2). Figure 2(a-c)** shows the adjusted association between NLA and SI in labour and postpartum women, including β-coefficients and 95% CI. After adjusting the multilevel model by age, nulliparity, and dilation, the mean SI without NLA across the measurements was 0.69, while in the NLA group, it was 0.76 (for a mean difference of 0.067).

Sensitivity analyses

We fitted models excluding women with PPH (**Figure S2**), transfusions (**Figure S3**), uterotonics (**Figure S4**), and assisted vaginal delivery (**Figure S5**). The SI difference in patients with and without NLA increased as labour progressed in each scenario.

DISCUSSION

The principal finding of our study was that during labour and the first two hours postpartum, SI increased significantly in patients with NLA compared to those without NLA. The difference between the groups remained significant after adjusting for confounders. The increase in SI was statistically and clinically significant, with a difference of 0.04 to 0.10 observed between groups (NLA and without NLA). According to previous references, the expected variation in SI in the postpartum period ranged from 0.7 to 0.9.[13–16.] Thus, a change in SI above a specific level of 0.9 implies significant blood loss, haemodynamic instability, and an increased risk of adverse outcomes. Although small, a change of 0.05-0.1 in SI is of substantial relevance in this setting.

Using a prospectively collected high-quality dataset from two hospitals, we describe the most extensive set of SI values gathered longitudinally in patients with and without NLA. A previous study by Nathan et al., which included 316 patients, noted that the SI was higher in those under NLA (33% of their sample). The authors suggested that epidural anaesthesia increased the mean SI by approximately 0.046.[31.] Other authors have explored the SI in obstetric patients without reporting the NLA percentage used in their population.[9,10,12,28]

Our data showed higher HR values during the postpartum period, with similar SBP among patients with NLA compared to those without obstetric analgesia. Extensive literature describes haemodynamic changes during pregnancy and delivery, including an increase in HR and a decrease in SBP at rest.[29] These adaptations are more pronounced during labour and the immediate postpartum period, probably due to pain, medications, and maternal anxiety.[30] During labour, uterine contractions displace 300–500 mL of blood from the uterus into the central circulation.[31] Immediately postpartum, there is an increase in cardiac output due to diminished lower extremity venous pressure, sustained myometrial contraction, and loss of low-resistance placental circulation.

Pregnancy increases the sympathetic system's dependency on maintaining haemodynamics, including the venous return and systemic vascular resistance. This situation means that pregnant patients are at an increased risk of hypotension and haemodynamic instability induced by neuraxial analgesia and anaesthesia. Despite the advantages of epidural analgesia over other techniques, this sympathetic block might explain some of the increase in SI in our patients. Furthermore, a compensatory mechanism needs to be activated in patients under NLA to maintain haemodynamics after a decrease in systemic vascular resistance, which generates a response based on a rise in HR.[22] Another potential explanation for the haemodynamic changes leading to a higher SI in patients under NLA might be the addition of some medications, such as uterotonics.[32,33] Several studies suggest that oxytocin induces a profound and transient decrease in both SBP and DBP during caesarean delivery secondary to vasodilatation, with tachycardia and an increase in cardiac output. This effect has been proposed as a secondary to peripheral vasodilation.[22,34,35]

In a study by Munn et al.[36], randomised women undergoing intrapartum caesarean delivery received a prophylactic infusion of oxytocin or bolus after delivery. A higher dose was associated with clinically significant tachycardia and hypotension (SBP of 100 mmHg or a decrease of [?] 20% from baseline).

The increase in heart rate reported during the early first and second stages of labour coincides with uterine contractions and bearing-down efforts. This change in heart rate might be explained by the displacement of blood from the choriodecidual space, increased venous return to the heart, and increased catecholamine release due to pain and other stimuli (anxiety). Additionally, during labour, uterine contraction pain becomes more pronounced during the transition to the second stage. This pain induces a neuroendocrine stress response, increasing heart rate and cardiac output.[37]

Our results show that SI values between groups with and without NLA were not modified by maternal age, parity, haemoglobin levels, gestational age, or cervical dilation. Similarly, a previous study by our group reported that labour, but not maternal anaemia, was associated with lower SI values during the first and second stages of labour compared to SI values in patients during the third trimester, possibly secondary to maternal pain and anxiety.[11]

Our study has several limitations. The main weakness is the nonrandomised and direct relationship between NLA exposure and SI between centres, given that only one of the centres includes NLA during labour. This

relationship may be inseparable from the association between the centre and SI. The unmatched analysis for oxytocin use limited an interpretation of the SI differences among the studied groups; consequently, we cannot explain whether NLA, oxytocin or both were the reasons for the significant differences in SI.

Additionally, the study design was restricted to pain management between the two clinical sites, implying differences in other interventions during labour, such as fluid management and other medications with potential influence on SI values. Despite this, we believe that the adjustments for clinical variables and the repeated measures analysis through labour and the postpartum period ameliorated biases associated with these differences in clinical practice. Another limitation was that almost all our patients were under the epidural technique; hence, the variation in SI observed should be interpreted cautiously in patients under NLA administered via different techniques. Other variables, such as top-up interventions for inadequate analgesia, duration of neuraxial analgesia, use of uterotonics other than oxytocin, and volume of blood loss, were not collected; therefore, adjustments for these possible confounders were not possible.

We did not consider the amount of blood loss in our analysis because our study did not focus on patients with PPH. However, we categorised patients according to the presence of PPH, without differences between the groups.

The strengths of this study are its prospective collection of data in different phases of the postpartum period for two groups (with and without NLA). Future studies should include a larger sample of patients with PPH and consider other potential confounders to establish reliable cut-off values for SI values.

CONCLUSION

SI increased during labour and the postpartum period in patients with NLA. Thus, different normal values should apply to patients in this condition. How this increase modifies the current threshold value of the SI in haemorrhagic shock assessment is still unknown.

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CONFLICT OF INTEREST

The authors declare no competing interests.

INDIVIDUAL CONTRIBUTION

JR and MV conceived and designed this research, drafted the manuscript and approved the final version. WO, JG, WA and FS led the recruitment of patients, helped write and critically revise the manuscript, and approved the final version. JM, AP, JS, and JC helped analyse the data, prepared the figures and table, wrote and critically revised the manuscript and approved the final version. NM, BR, and MN helped recruit patients, critically revised the manuscript, interpreted the data and approved the final version.

DETAILS OF ETHICS APPROVAL

The Institutional Review Board and Ethics Committee from the University of Cartagena (Cartagena de Indias, Colombia) approved this study (Ethical Committee No. 022/2017) on 16 May 2017. Additionally, each recruitment centre reviewed and approved the study before the start of data recruitment.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (JR - joseantonio.rojas.suarez@gricio.com). The data are not publicly available due to privacy or ethical restrictions.

TRANSPARENCY STATEMENT

The corresponding author (JR) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Clinical characteristics, interventions, and clinical outcomes of the study groups.

Characteristics	**Without neuraxial labour analgesia (n=294)**	**With neuraxial labour analgesia (n=228)**	**P**
Maternal age (years)	23 [20–28]	25.5 [21–30]	<.001
Nulliparity	81 (27.6%)	97 (42.5%)	<.001
Pre-gestational BMI (kg/m^2)	23.1 [21.1–25.1]	23.6 [21.6–25.3]	.35
Gestational age at delivery (weeks)	39 [38–40]	39 [38–40]	.08
Haemoglobin level (gr/L)	11.2 [10.6–12]	13.1[2.5–13.9]	<.001
Cervical dilation (cm)	9 [8–10]	5 [4–6]	<.001
Neuraxial Analgesia			
Epidural	0	219 (96.1%)	N/A
Spinal	0	2 (0.9%)	N/A
Combined (spinal-epidural)	0	6 (2.6%)	N/A
Outcomes			
Postpartum haemorrhage	3 (1%)	6 (2.6%)	.16
Transfusion of blood products	1 (0.3%)	3 (1.31%)	.23
Coagulopathy	0	0	N/A
Referral to a higher-level facility or ICU admission	1 (0.3%)	1 (0.4%)	.85
Maternal death	0	0	N/A

BMI: Body mass index; N/A, no statistical test was performed.

Data are n (%), or median [95% confidence limit] unless otherwise specified.

Table 2. Mean (Standard Deviation) of Shock index values during labour and the postpartum period stratified by analgesia status (With and Without Neuraxial labour analgesia)

Timing	Without neuraxial labour Analgesia (n=294)	With neuraxial labour Analgesia (n=228)	P
Antepartum measures			
First stage of labour	0.70 ± 0.10	0.74 ± 0.13	<.001
Second stage of labour	0.70 ± 0.11	0.78 ± 0.16	<.001
Postpartum measures			
30 minutes	0.68 ± 0.10	0.78 ± 0.16	<.001
60 minutes	0.68 ± 0.09	0.79 ± 0.15	<.001
90 minutes	0.68 ± 0.11	0.78 ± 0.15	<.001
120 minutes	0.68 ± 0.10	0.78 ± 0.1	<.001

Data are mean ±SD (%), unless otherwise specified.

FIGURE LEGENDS

Figure 1 . A longitudinal analysis with repeated measures of SI was performed using a linear mixed-effects model. The change in SI during labour and postpartum was the primary outcome. The crude trends and the 95% CI of the multilevel regression model across repeated measures for SI, HR, and SBP are shown. The mean raw values of SI, HR and SBP are also presented.

Figure 2. An adjusted linear mixed-effects model was performed by maternal age (older than 35 years), haemoglobin level, cervical dilation, and nulliparity. For continuous (except for cervical dilation) variables, we stratified and entered them as dummy indicators in the multilevel model. Additionally, the models were fitted for each component of the SI (HR and SBP).

SUPPORTING INFORMATION

Appendix S1. Description of spinal analgesia protocol during labour (CUB)

Table S1. Missing data among the most relevant variables.

Table S2. Beta coefficients of fixed effects of multilevel model.

Figure S1. Flowchart of patient enrolment.

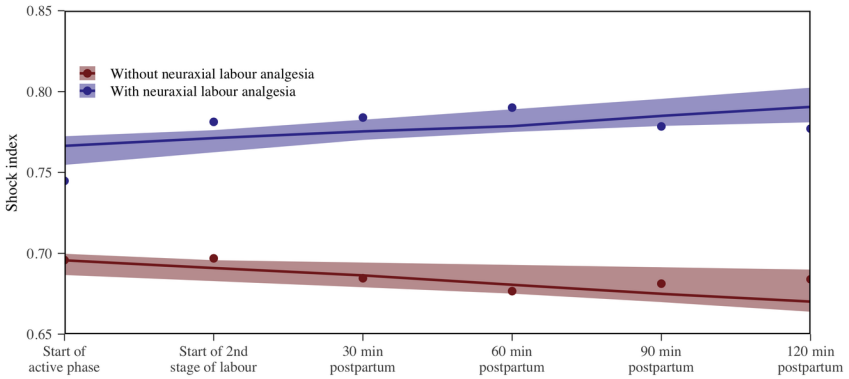
Figure S2. Adjusted Multilevel – Sensitivity analysis (no PPH).

Figure S3. Adjusted Multilevel – Sensitivity analysis (no transfusions).

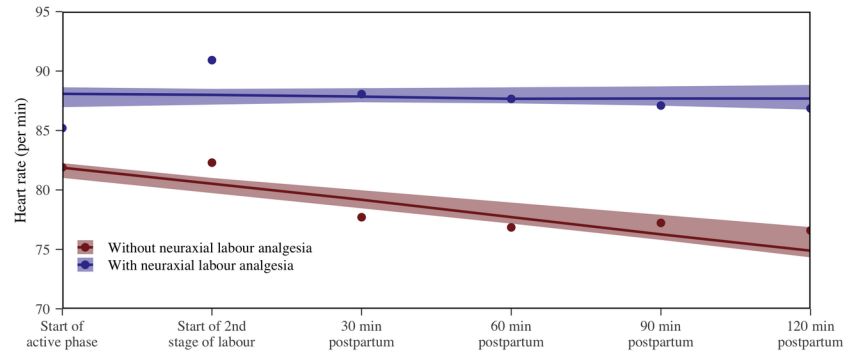
Figure S4. Adjusted Multilevel – Sensitivity analysis (no uterotonics).

Figure S5. Adjusted Multilevel - Sensitivity analysis (nonuse of assisted vaginal delivery).

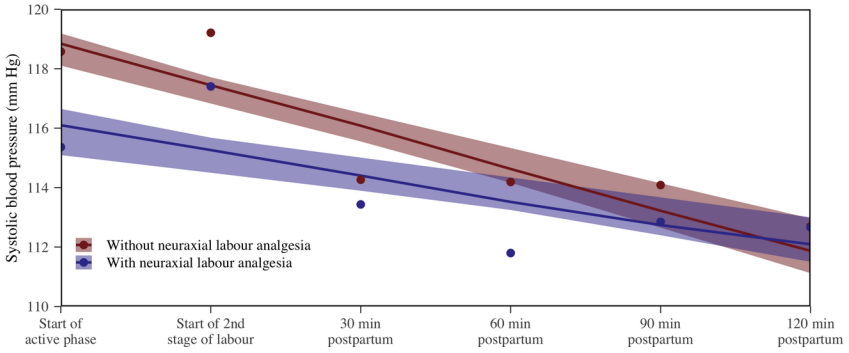
A. Shock index.



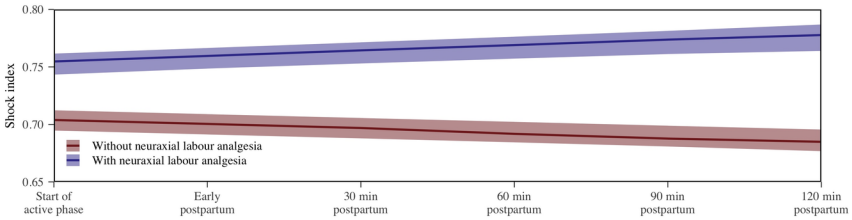
B. Heart rate.



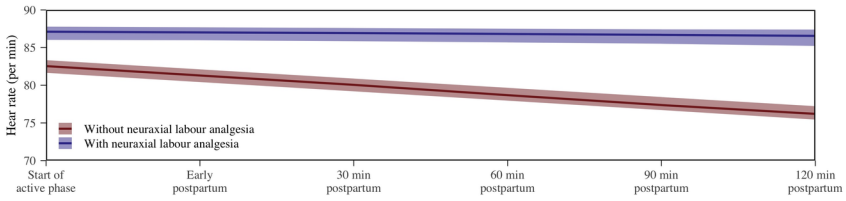
C. Systolic blood pressure.



A. Shock index.



B. Hear rate.



C. Systolic blood pressure.