

# Possible Impact of Spinal Anesthesia and Phenylephrine on Sublingual Microcirculation of Cesarean Delivery Patients

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## Abstract

**Background:** This study was a proof of concept of a novel means to evaluate microcirculatory changes during spinal anesthesia for cesarean delivery. It sought to examine the distributive circulatory effects of spinal anesthesia and evaluate the impact of phenylephrine administration on the microcirculation of these women.

**Methods:** After Research Ethics Board approval, healthy, non-laboring pregnant women with singleton, term pregnancies scheduled for elective cesarean delivery were recruited. Participants were randomly assigned to receive either phenylephrine infusion or phenylephrine bolus. Spinal anesthesia was standardized. A sidestream dark-field (SDF) MicroScan<sup>®</sup> video microscope was applied to the sublingual mucosa to obtain microcirculation videos in five different visual fields. Videos were made before and after spinal anesthesia. The resultant videos were analyzed randomly and blindly. The mean microvascular flow index (MFI) values were compared before and after spinal anesthesia. The difference in MFI following spinal anesthesia was compared between phenylephrine infusion and bolus groups.

**Results:** Thirty-two patients were recruited for the study; 22 patients had complete video sets for analysis. Baseline characteristics were similar between the two groups, including preoperative hemodynamics. There were no significant differences between pre- and post-spinal MFI. The post-spinal MFI within the infusion group (mean  $\pm$  standard deviation:  $2.74 \pm 0.21$ ) was not significantly different from the bolus group ( $2.56 \pm 0.42$ ,  $P = 0.22$ ).

**Conclusion:** Despite theoretical physiological implications of spinal anesthesia and phenylephrine on the microcirculation, significant alteration of the MFI was not observed between pre- and post-spinal

anesthesia (within group). Additionally, despite an eight-fold larger phenylephrine dose for continuous infusion prophylaxis used in this group of women, this did not result in a significant alteration of the microcirculation compared to those who received phenylephrine treatment for hypotension (between groups).

**Keywords:** Spinal anesthesia; Microcirculation; Phenylephrine; Sidestream dark-field imaging; Obstetric anesthesia

## Introduction

Maternal hypotension is the most common side effect of spinal anesthesia and is a result of physiologic changes to the macrocirculation [1, 2]. Spinal anesthesia causes sympathetic nervous system blockade and reduction of systemic vascular resistance. Maternal hypotension is associated with adverse side effects such as maternal nausea and vomiting and fetal acidosis from reduced placental blood flow (secondary to maternal hypotension). If maternal hypotension is treated and/or prevented with vasopressors, specifically the direct  $\alpha$ -adrenergic agonist, phenylephrine, fetal outcomes as assessed by umbilical arterial and venous pH are significantly improved [1, 3-6]. These fetal improvements are likely due to the vasopressor effect on the maternal microcirculation and its subsequent impact on macrocirculation and central hemodynamics [7, 8].

The microcirculation, consisting of the smallest vessels of the vasculature, is responsible for delivery of oxygen and regulation of blood pressure. Microcirculation by definition includes capillaries, small arterioles and venules which connect immediately adjacent to capillaries to form the pre- and post-capillary units [9]. Currently, our understanding of changes to the microcirculation in pregnant women receiving spinal anesthesia for cesarean delivery is limited. The impact of spinal anesthesia and phenylephrine on the microcirculation of pregnant women using sidestream dark-field (SDF) technology is yet to be reported. This novel study is the first to analyze the microcirculatory response in patients who receive spinal anesthesia and receive two variations of phenylephrine administration for treatment. Abdo et al stated that SDF imaging is a novel approach to the measurement of microcirculation and has a wide application of usefulness within the clinical field [10].

SDF imaging is a stroboscopic light-emitting diode (LED) ring-based imaging modality allowing microscopic assessment

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of microcirculatory capillary density and perfusion in clinical settings [11-13]. This is achieved by an analysis of the moving cells in the images, which permits the quantitative measurement of red blood cell flow in the capillaries. SDF imaging consists of a light guide surrounded by a 530 nm LED, a wavelength of light that is absorbed by the hemoglobin of red blood cells, which allows for their observation as dark cells flowing in the microcirculation. It permits quantification of microvascular blood flow using the microvascular flow index (MFI) and vessel density.

The primary objective of this research was to examine the physiologic impact of spinal anesthesia and the influence of prophylactic phenylephrine infusion (PEI) versus phenylephrine bolus (PEB) administration on the distributive circulation. This objective was measured by SDF imaging on the sublingual microcirculation of pregnant subjects. The SDF imaging was performed pre- and post-spinal anesthesia, prior to neonatal delivery during cesarean delivery. We also compared the influence of PEI administered for prophylaxis to PEB administered for treatment of hypotension on sublingual microcirculation following administration of spinal anesthesia. We hypothesized that the combined impact of spinal anesthesia and phenylephrine on the microcirculation would be a reduced MFI, vascular density and proportion of perfused vessels.

## Materials and Methods

With Institutional Research Ethics Board approval (IWK REB #1010276), ASA physical status II pregnant women with singleton gestation at gestational age > 36 weeks scheduled for elective cesarean delivery under spinal anesthesia were recruited. This study was conducted in compliance with the ethical standards of the IWK Health Centre on human subjects as well as with the Helsinki Declaration. Patients were recruited at the IWK Health Centre, Halifax, NS, Canada. Exclusion criteria included: women who were in labor, had a body mass index (BMI) > 35 kg/m<sup>2</sup>, type 1 diabetes mellitus, hypertensive disease or cardiac disease, an allergy to phenylephrine or any other standardized medication, were smokers, or had any caffeine intake within 6 h of SDF measurement. Patients were withdrawn if they were unable to complete the SDF imaging or if they had a failed spinal anesthetic (i.e. block lower than T6 dermatome or greater than T2 dermatome). Block height was determined with a blunt tip needle approximately 5 min after spinal anesthetic was administered.

After informed consent was obtained, patients were randomly assigned to one of two groups: PEI or PEB. Patient allocation was performed by opening opaque envelopes containing the patient's group and study ID number prepared by research staff. Randomization was according to a computer-generated randomization order (Random.org). Maternal age, height, weight, BMI and gestational age were recorded. Blood pressure and heart rate were measured in the supine position with left uterine displacement. Baseline systolic blood pressure (SBP) was determined by calculating the mean of three consecutive SBP measurements taken in the preoperative area.

All patients received antacid prophylaxis with 30 mL so-

dium citrate and were transferred to the operative room. Spinal anesthesia was clinically administered at the L3-L4 interspace in the sitting position using 12 mg of hyperbaric bupivacaine with 15 µg of fentanyl and 150 µg of preservative free morphine. Patients were then immediately laid supine with left uterine displacement to minimize aortocaval compression and hypotension. All patients received a crystalloid fluid co-load immediately after the spinal. This was gravity delivered with a goal of 1,000 mL prior to delivery. The dermatomal level affected was determined 5 min after spinal anesthesia by the attending anesthesiologist and recorded. Blood pressure was measured at 1-min intervals for the first 15 min immediately after the spinal anesthetic, then every 2.5 min until the time of delivery. Hypotension was defined as the higher blood pressure of either SBP < 80% of baseline or < 90 mm Hg. Hypertension was defined as SBP > 120% of baseline.

Patients in the PEI group had a PEI of 30 µg/min started immediately after administration of spinal anesthesia in conjunction with crystalloid fluid co-loading. Participants in the PEB group were also given the same crystalloid co-load after the spinal was administered. Those in the PEB group who experienced hypotension (range predefined) were treated with 50 - 100 µg boluses of phenylephrine (5 - 10 mg boluses of ephedrine second line therapy). The number and type of interventions needed to maintain the blood pressure in the patients' target range were documented. The total amount of intravenous fluid administered, as well as the total cumulative dose of vasopressors administered during the study period, was also recorded.

The initial SDF measurements were completed in the obstetric preoperative area with the patient supine with left uterine displacement, mirroring the position in the operating room. The second set of paired post images were then completed 10 min after spinal anesthesia was initiated. Trained research staff recorded all noninvasive SDF images using the MicroScan<sup>®</sup> video microscope (MicroVision Medical, Amsterdam, The Netherlands). The SDF device was equipped with a sterile LED probe cap and was gently applied to the sublingual oral mucosa to avoid pressure artifact. Steady images of at least 10 s duration were recorded and stored digitally on a research laptop. Digital recordings of five different visual fields were obtained for each participant, with minimal intervals between recordings.

Research staff quantified blood flow using semi-quantitative analysis software (AVA 3, MicroVision Medical) which was developed specifically for the MicroScan<sup>®</sup> video microscope. Video clips were analyzed by the same, single research staff according to the established guidelines [14]. The video images, which contain no identifiable information, were analyzed at random to prevent coupling between images. An investigator not involved with the video analysis completed the randomization of the videos with a randomization table generated on Random.org separate from the participant allocation randomization. Demographic and clinical data were collected and presented as mean (standard deviation), median (interquartile range), or counts as appropriate using SPSS Statistic 21 software package (IBM Corporation, Armonk, NY, USA).

The primary outcome was MFI pre- and post-spinal anesthesia. Additionally, comparison of the impact of vasopres-

**Table 1.** Demographic Characteristics

	Phenylephrine infusion (n = 11)	Phenylephrine bolus (n = 11)	P-value
Age (years)	32 ± 5	34 ± 5	0.31
BMI (kg/m <sup>2</sup> )	29 ± 3	29 ± 3	0.88
Gestational age (weeks)	39 ± 1	39 ± 1	0.57
Gravidity	2 (2 - 3)	2 (1 - 3)	0.71
Parity	1 (1 - 1)	1 (0 - 1)	0.42
Baseline SBP (mm Hg)	113 ± 6	117 ± 10	0.09

Data presented as mean ± SD or median (IQR). BMI: body mass index; SD: standard deviation; IQR: interquartile range; SBP: systolic blood pressure.

sors administered either PEI vs. PEB post-spinal anesthesia on MFI was assessed. A power calculation was performed for the difference between two dependent (pre- and post-spinal) and secondarily, two independent (PEI and PEB groups) means of MFI using data from our recently completed assessment of maternal microcirculation [15]. Using G\*Power (version 3.0.10, University of Dusseldorf) with a standard deviation of 0.2, the calculated effect size is 1.472 (10% change in capillary density) (alpha 0.05, power 0.9). Eight (dependent) or 24 (independent) patients (12 per group) result in the appropriate power. The mean MFI values of all patients were compared before and after spinal anesthesia using paired Student's *t*-tests.

## Results

Thirty-two participants were recruited and randomly assigned to either receive a PEI or PEB. Of these, 22 patients had complete video sets available for pre- and post-spinal analysis and of these, assigned to either receive a PEI (n = 11) or PEB if treatment was required (n = 11).

Baseline characteristics were similar between the two groups, including preoperative hemodynamics (Table 1). Intraoperative characteristics are presented in Table 2. The mean dose of phenylephrine in the PEI group was 1,603 ± 470 µg with four patients who experienced hypotension requiring the rate of PEI to be increased. Hypotensive characteristics were identified if a patient's SBP decreases to < 90 mm Hg, or a decrease by 20% in SBP. Of those four, the infusion rate was increased prior to imaging in three patients, and after imaging in one patient. One patient received an additional 10 mg ephedrine to treat hypotension. Nine patients in the PEB group received vasopressors during the 10-min evaluation period with mean doses of 200 ± 142 µg of phenylephrine and 13 ± 6 mg of ephedrine.

**Table 2.** Intraoperative Characteristics

	Phenylephrine infusion (n = 11)	Phenylephrine bolus (n = 11)	P-value
Duration of surgery (min)	53 ± 27	43 ± 9	0.15
Total fluids given (mL)	1,559 ± 412	1,891 ± 419	0.08
Estimated blood loss (mL)	586 ± 158	500 ± 140	0.19

Data presented as mean ± SD. SD: standard deviation.

The pre-spinal MFI (2.78 ± 0.27) was not significantly different than the post-spinal MFI (2.65 ± 0.34) for all participants (mean difference (MD): 0.13, 95% CI: -0.03 to 0.29, P = 0.11, Fig. 1). There were no significant differences between pre- and post-spinal MFI in the within-group comparisons (Fig. 2a (PEI) and b (PEB)). The between-group comparison of post-spinal MFI for the PEI group (2.74 ± 0.21) was not significantly different compared to the post-spinal PEB group (2.56 ± 0.42) (MD: 0.18, 95% CI: -0.11 to 0.48, P = 0.22, Fig. 3). There were no differences in total vessel density, perfused vessel density, or the proportion of perfused vessels between the PEI and PEB groups following administration of spinal anesthesia (Table 3).

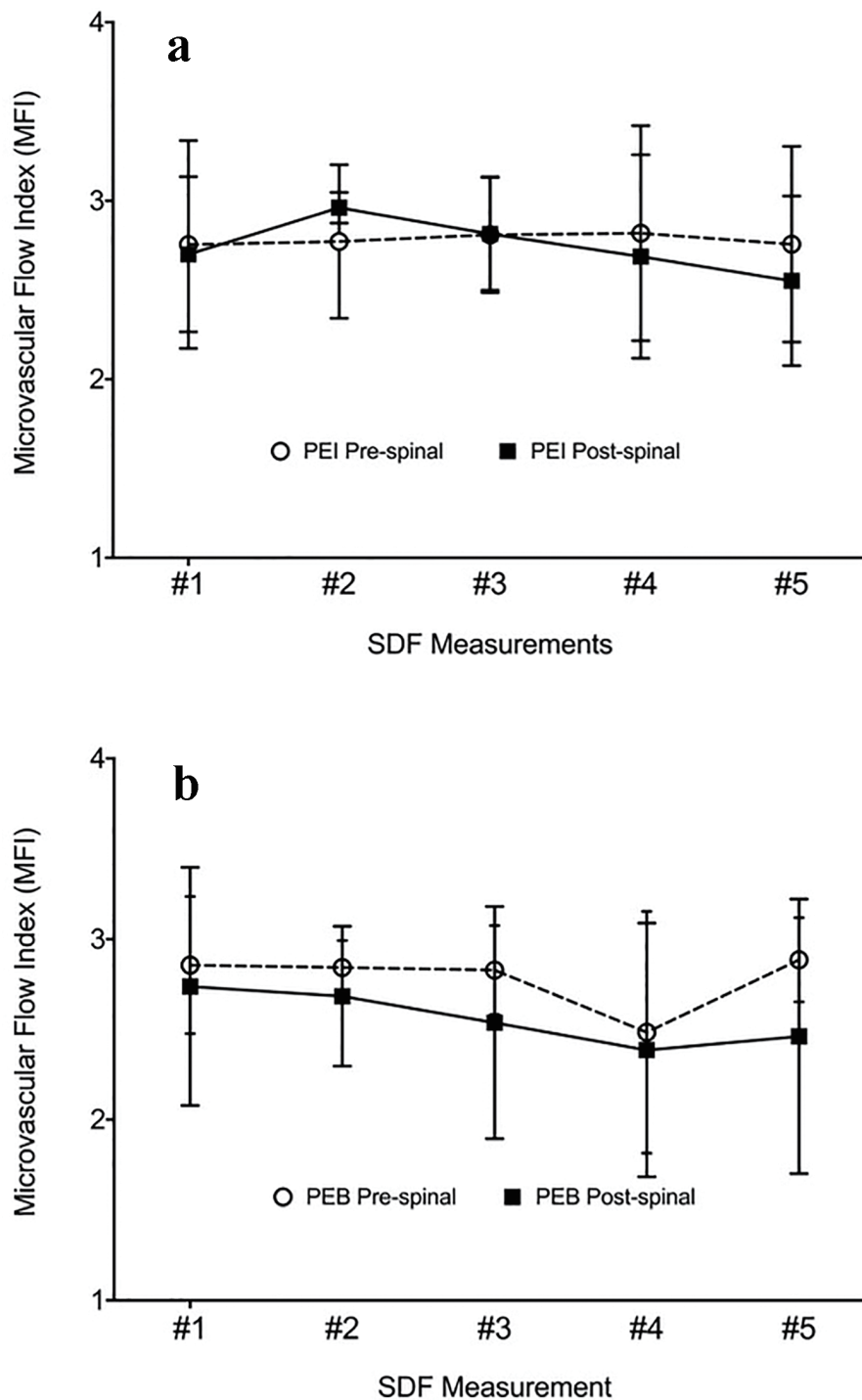
Within the PEB group, seven participants received vasopressors prior to imaging, two participants received vasopressor after imaging and two did not receive any vasopressors. Subgroup analyses were conducted comparing the four subjects who did not receive vasopressors prior to imaging, to the seven subjects who did. This showed there was no significant difference between the mean MFI pre- (MD: -0.06, 95% CI: -0.38 to 0.25, P = 0.66) and post-spinal (MD: 0.17, 95% CI: -0.45 to 0.79, P = 0.56).

## Discussion

This study was designed to improve our understanding of how spinal anesthesia and phenylephrine influence maternal microcirculation. Our results showed no statistically significant difference in MFI after administration of spinal anesthesia (Fig. 2). This suggests that spinal anesthesia may have a limited impact on sublingual microcirculation. These findings are congruent with a recent report from our group showing that epidural analgesia may not impact sublingual microcirculation in laboring women [16].



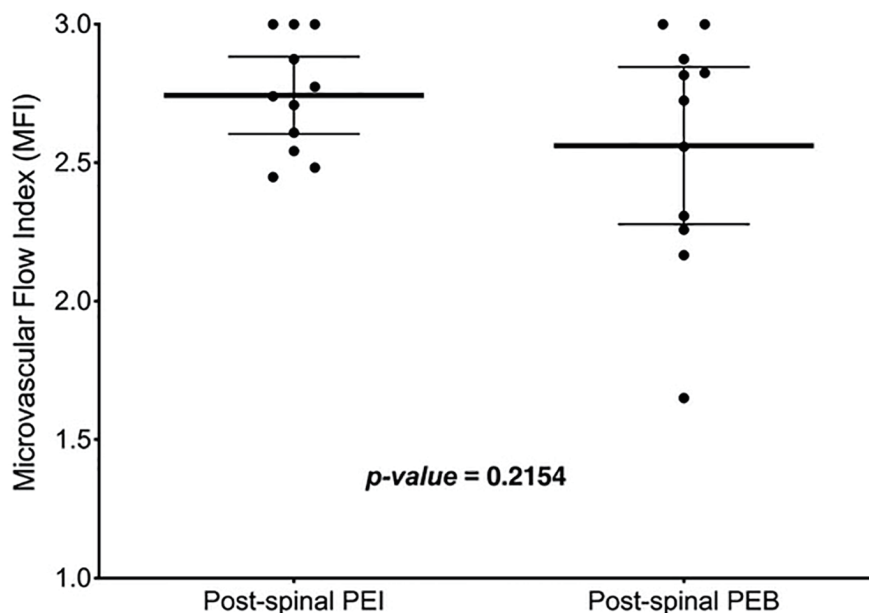




**Figure 2.** MFI measurements pre- and post-spinal anesthesia for the (a) phenylephrine infusion and (b) phenylephrine bolus groups.

Due to technical issues with SDF video quality, we were unable to capture the required 12 participants per group ( $n = 11$ ) as determined *a priori* to detect a significant difference pre-post spinal anesthesia between PEI and PEB groups. The technical challenges included suboptimal imaging of the capillaries due to motion-induced image blurring by movement of

the OPS device, the tissue and/or flowing red blood cells. Also, in larger vessels, especially during continuous flow, it is difficult to observe the granular nature of flowing blood cells due to blurring of images. These technical challenges introduce difficulties in measuring blood flow velocities in these vessels. For these reasons, recruitment was halted at 32 subjects.



**Figure 3.** Post-spinal MFI between infusion and bolus groups was not significantly different ( $P = 0.22$ ). Thick, solid line in the box represents the mean, whiskers represent the 95% confidence interval and solid dots are participants. MFI: microvascular flow index.

While providing important insight, this study was limited by its clinical nature and the necessity to treat hypotension for safety and symptomatic control. These necessary safety protocols limited our ability to control for the amount and timing of phenylephrine patients received and therefore it can be difficult to isolate the influence of spinal anesthesia on microcirculation when confounded by vasopressor. This influence should be further explored using a gravid animal model, where maintenance of normal blood pressure and symptom management is not a requirement, thus allowing a better comparison. Additionally, we have not attempted to measure the contribution of macrovascular changes in the response to spinal anesthesia or phenylephrine. The measurements may have helped us to correlate their influence with hemodynamic changes. Lastly, the hemoglobin level, which was not measured, appears to be a determinant of the capillary network and may impact the sublingual capillary density [20]. Future studies incorporating a positive control, such as a large vessel, and measuring hemoglobin levels may elucidate the influence of vasopressors or fluid resuscitation.

In conclusion, we have found no difference in MFI before or after administration of spinal anesthesia, nor between groups receiving phenylephrine as a prophylactic infusion or in required treatment boluses. These findings suggest that nei-

ther spinal anesthesia nor PEI at 30  $\mu\text{g}/\text{min}$  have a strong influence on microcirculatory blood flow. By extension, consideration of these practices likely does not pose a significant risk when providing regional anesthesia and hemodynamic support during cesarean delivery.

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### Conflict of Interest

The authors have no conflict of interest to disclose.

**Table 3.** Additional Post-Spinal Microcirculation Measures

	Phenylephrine infusion (n = 11)	Phenylephrine bolus (n = 11)	Mean difference (95% CI)	P-value
Total vessel density	22.9 $\pm$ 4.1	23.3 $\pm$ 4.0	-0.4 (-4.4 to 3.6)	0.80
Perfused vessel density	21.2 $\pm$ 4.1	19.7 $\pm$ 4.3	1.5 (-2.2 to 5.3)	0.40
Proportion of perfused vessels	92.9 $\pm$ 6.8	85.3 $\pm$ 15.6	7.6 (-3.1 to 18.3)	0.15

CI: confidence interval.

## Informed Consent

All patients provided written informed consent prior to study participation.

## Author Contributions

Ronald George contributed to the conception and design of the study, data analysis and writing of the manuscript. Colin Boyd contributed to the data collection, data analysis and writing of the manuscript. Dolores McKeen contributed to the design of the study, data interpretation and editing of the manuscript. Islam Saleh Abdo contributed to the design of the study, data interpretation and editing of the manuscript. Christian Lehmann contributed to the design of the study, data interpretation and editing of the manuscript.

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