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ORIGINAL ARTICLE

A pilot study of the pleth variability index as an indicator of volume-responsive hypotension in newborn infants during surgery

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Abstract
Purpose The aim of this pilot study was to evaluate the diagnostic value of pleth variability index (PVI) to predict fluid responsiveness in newborn infants during surgery.
Methods PVI was continuously recorded in 29 mechanically ventilated newborn infants during surgery, and episodes of clinically indicated volume expansion (VE) ($\geq$10 ml/kg in $\leq$15 min) administration were evaluated. The upper limit of the reference range for PVI in mechanically ventilated newborns was defined by the 95th percentile of all PVI values from hemodynamically stable infants.
Results The upper limit of the reference range of PVI was 18 %. One hundred and three VEs were evaluated in 58 sufficient VE size (SVES) episodes and 16 insufficient initial VE size (IVES) episodes requiring repeated VE; all but one fulfilled criteria of volume-responsive hypotension (VRH). The median (interquartile range) PVI value during arterial hypotension in the 73 episodes with VRH was 23 % (20–25 %); postvolume PVI was 16 % (13–18 %). In 63 of 73 VRH episodes, during-hypotension PVI values were >18 % (86 % sensitivity for VRH). The median intermediate PVI, measured between VE in IVES episodes, was significantly higher than post-VE PVI in SVES episodes [18 % (16–21 % vs. 16 % (13–18 %].
Conclusion This preliminary evaluation shows that PVI may indicate VRH in newborn infants during surgery.

Keywords Newborn · Fluid responsiveness · Noninvasive monitoring · Plethysmography · Surgery

Abbreviations

IVES	Insufficient initial volume expansion size
PI	Perfusion index
ΔPOP	Variations in pulse oximetry plethysmographic waveform amplitude
PP	Pulse pressure
PVI	Pleth variability index
SVES	Sufficient volume expansion size
VE	Volume expansion
VRH	Volume-responsive hypotension
MABP	Mean arterial blood pressure

Introduction

During surgery, arterial hypotension is a common finding and is frequently caused by hypovolemia. Consequently, volume expansion (VE) is often the first therapy applied to improve hemodynamics should arterial hypotension occur. Maintaining adequate preload while avoiding excessive VE will maintain cardiovascular stability, organ perfusion, and adequate tissue oxygenation [1]. Recently published studies show that in adults, judicious fluid management in the operating room is able to reduce the length of hospital stay,

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morbidity, and mortality after major surgery in various settings [2, 3]. During surgery, clinical signs suggesting hypovolemia, such as tachycardia, poor peripheral perfusion, or poor urine output may either be unspecific or cannot be monitored adequately. Perioperative monitoring for potential fluid responsiveness aims to avoid ineffective or even deleterious VE. Static indices of cardiac preload, such as central venous pressure and pulmonary artery wedge pressure, poorly predict the response to VE [4, 5]. Dynamic indices, such as pulse-pressure and stroke-volume variations, which are based on respiratory variations in left ventricular stroke volume, are increasingly used to detect the cyclic respiratory fluctuation of the arterial pressure wave in the mechanically ventilated patient in order to predict fluid responsiveness [6–8]. However, these dynamic indices are either invasive, requiring additional catheters; unavailable in the pediatric and particularly the neonatal population; or operator dependent.

Noninvasive indices, such as the respiratory variations in pulse oximetry plethysmographic waveform amplitude (ΔPOP), predict fluid responsiveness in mechanically ventilated patients [9]. However, plethysmographic waveform analysis, requiring specific tools and software, is currently unavailable for continuous bedside monitoring [10]. The recently introduced Masimo Radical-7 monitor (Masimo Corp., Irvine, CA, USA) provides an automatic, noninvasive, and continuous estimate of ΔPOP by calculating the pleth variability index (PVI).

Although there have been clinical investigations into the ability of PVI to predict fluid responsiveness in infants, children, and adults [11–13], PVI accuracy has not yet been evaluated in newborn infants undergoing surgery. Predicting fluid responsiveness with such a noninvasive device would permit maintaining adequate preload and avoiding excessive VE while avoiding an invasive monitoring in newborn infants. Therefore, the purpose of this pilot study was to evaluate the ability of PVI to predict fluid responsiveness in newborn infants during surgery.

Materials and methods

The protocol was approved by the Ethics Committee of the University of Bonn, the study was performed in accordance with the Declaration of Helsinki, and written informed parental consent was obtained the day before surgery.

Patients

To standardize documentation, newborn infants were admitted in this pilot study if study persons (SB and AM) were available to perform the study protocol during surgery. The study was carried out in 29 mechanically ventilated preterm ($n = 13$) and term ($n = 16$) newborn infants undergoing minor or major surgery between October 2009 and September 2010: congenital diaphragmatic hernia (repair of diaphragmatic eventration) ($n = 1$), duodenal atresia ($n = 3$), anal atresia ($n = 3$), gastroschisis ($n = 2$), omphalocele ($n = 5$), necrotizing enterocolitis ($n = 5$), ileus ($n = 2$), ileostomy closure ($n = 4$), myelomeningocele ($n = 2$), encephalocele ($n = 1$), and Rickham reservoir placement for hydrocephalus ($n = 1$). Their median and interquartile range (IQR) postmenstrual age and weight at the time of surgery was 37 (34–40) weeks and 2,320 g (1930–3080 g), respectively. Patients with cardiac disease, including arrhythmia, intracardiac shunt, and heart failure, were a priori excluded. All infants were ventilated to achieve adequate blood gas values at minimal fractional inspiratory oxygen (FiO_2), ventilator pressure, and tidal volumes (in general, 4–6 ml/kg) in the pressure-controlled mode. Attending physicians were asked not to change ventilator settings within 3 min before, during, and until 3 min after VE, if possible. Fifteen of 29 (52 %) patients had already been on inotropes before surgery and data acquisition onset.

Volume expansion

VE (defined as any crystalloid fluid challenge of ≥10 ml/kg or colloid fluid challenge of ≥5 ml/kg within ≤15 min i.v.) were administered at the discretion of the attending physician (SB and AM).

Definition of hypotension

In an approximation of data from preterm and term newborn infants [14–16], the definition of normal mean arterial blood pressure (MABP) for this study was gestational age at birth in weeks + postnatal age in days during the first week of life up to 40 mmHg. Temporary hypotension according to this definition did not necessarily trigger VE, as it may be caused by several other factors, and the decision to administer fluids was entirely left to the attending physician, as described below.

Definitions of fluid-responsive hypotension and sufficient versus insufficient VE size

Volume-responsive hypotension (VRH) was a priori defined as an increase in MABP by >10 % following VE. Only episodes without simultaneous inotropic support or with constant infusion rates of inotropes within 3 min before and after VE were recorded. If repeated VE were required within ≤3 min, these were combined within one episode and evaluated together. These episodes of repeated VE were classified as insufficient initial VE size (IVES)

episodes, whereas episodes without additional VE within ≤3 min were defined as sufficient VE size (SVES) episodes. In SVES episodes, the median (IQR) time interval to the next VE episode was 10 (5–20) min. The 3-min time interval for the definition of IVES vs. SVES episodes was deduced from the averaging time of PVI readings, as described below.

Intraoperative monitoring

Heart rate by electrocardiogram (ECG) and oxygen saturation by pulse oximetry were continuously monitored using an M3 multiparameter monitor (Philips, Böblingen, Germany). Blood pressure was measured noninvasively in two infants using the M3 multiparameter monitor and invasively via peripheral arterial lines in 30 infants using the same monitor.

Pleth variability index calculation

PVI was measured using a Masimo Radical 7 pulse oximeter. PVI data were downloaded from the internal trend memory of the device to a standard computer using proprietary software Trendcom provided by Masimo. The sampling rate was 0.1 Hz. A neonatal LNCS sensor was used, which was placed on either a hand or a foot. PVI is a measure of the dynamic change in perfusion index (PI) that occurs during a complete respiratory cycle and is described in detail elsewhere [17]. Briefly, the PI is a scaled numerical value calculated as the percentage between the infrared pulsatile [alternating current (AC)] signal and the nonpulsatile [direct current (DC)] infrared signal (PI = [AC/DC] × 100), reflecting the amplitude of the pulse oximetry plethysmographic waveform. Then, PVI is calculated by measuring changes in PI over a time interval of approximately 15 s, sufficiently long to include several complete respiratory cycles, as $PVI = [(PI_{max} - PI_{min})/PI_{max}) \times 100]$. For this study, PVI averaging time was set to the short time position, and the derived PVI values were averaged over a time period of 2–3 min; one value was recorded every 10 s. The attending physician was not blinded to the PVI so that he could monitor the hemoglobin oxygen saturation (SpO_2) reading, if required, but was discouraged to pay attention to the PVI reading as the meaning of the displayed value was unknown, a reference range for PVI had not been established, and the averaging time interval was known to be long.

Defining a reference range of PVI in neonates during surgery

For this pilot study, the PVI cutoff value was defined by the 95th percentile of all PVI values recorded in 20,740 s (345 min) in five hemodynamically stable newborn infants [gastroschisis ($n = 1$), omphalocele ($n = 1$), ileus ($n = 1$), encephalocele ($n = 1$), Rickham reservoir placement for hydrocephalus ($n = 1$)] who received no VE or any other cardiovascular intervention during surgery.

Prehypotension PVI, during-hypotension PVI, intermediate PVI, and post-VE PVI

Hemodynamic alterations based on changes in fluid status seem to occur rapidly in small infants. On the other hand, the PVI averaging time interval of the device was relatively long at 2–3 min, explaining why in our study population, the median (IQR) time interval between onset of arterial hypotension and maximal PVI value was (2–4)] min. The length of the time intervals for determining mean PVI values was arbitrarily chosen to be 3 min to: (a) take into account for the relatively long averaging time for PVI values of 2–3 min implemented in the device, as explained above; and (b) avoid interference caused by the attending anesthetist's interventions. To enable a meaningful, reproducible comparison of PVI values before VE, during arterial hypotension, and after VE, we calculated for each VE administration the mean PVI value within 3 min before arterial hypotension onset as prehypotension PVI, mean PVI value within 3 min after arterial hypotension onset for PVI during arterial hypotension (during-hypotension PVI), and mean PVI within 3 min after the end of VE for post-VE PVI. In the 16 IVES episodes with repeated VE within ≤3 min, post-VE PVI values were determined after the last VE of this episode. In these IVES episodes, an intermediate PVI value was calculated as the mean PVI value within 3 min after the initial, inadequately sized, VE.

Statistical analysis

Data are expressed as median (IQR). Statistical analysis was performed by SPSS 18.0 (SPSS Inc., Chicago, IL, USA) software package for Windows. The Mann–Whitney *U* test was used for between-group comparisons. The nonparametric Wilcoxon signed-rank tests for paired samples were used for within-group comparisons. Differences at the level of $p < 0.05$ were considered to be statistically significant. For sensitivity, an exact 95 % confidence interval (CI) was calculated.

Results

The upper limit of PVI value reference range defined as the 95th percentile of all PVI values in five hemodynamically stable neonates undergoing surgery was 18 %. One hundred and three VE administrations were recorded in 24

Table 1 Distribution of volume expansion (VE) episodes during surgery

Type of VE episode	No. of additional VE within 3 min	No. of VE episodes (74)	No. of VE (100[b])	Measures determined
SVES	0	58[a]	58	Prehypotension PVI, during-hypotension PVI, post-VE PVI
ISVES	1	10	20	Prehypotension PVI, during-hypotension PVI, intermediate PVI (1 each), post-VE PVI
	2	4	12	Prehypotension PVI, during-hypotension PVI, intermediate PVI (2 each), post-VE PVI
	4	2	10	Prehypotension PVI, during-hypotension PVI, intermediate PVI (4 each), post-VE PVI
			[b]	

VE volume expansion, *SVES* sufficient VE size, *IVES* insufficient initial VE size, *PVI* pleth variability index

[a] 57 of 58 SVES episodes and 16 of 16 IVES episodes fulfilled criteria of volume-responsive hypotension

[b] Three additional VE episodes were excluded from analysis because of simultaneous change in inotropic therapy

infants during surgery; three were excluded from analysis because of simultaneous onset or change of administration of inotrope or vasopressor therapy, with suspicion that the PVI readings were affected by this concomitant therapy and did not reflect effects of VE administration only. In 58 episodes, VE was considered of adequate size by the attending physician, and no further VE was administered within the next 3 min [median (IQR) time interval between VE episodes; 10 (5–20) min]. In 16 episodes, repeated VE (IVES, $n = 42$) administrations were required within 3 min of the previous one until VE was clinically considered to be adequate (Table 1).

Seventy-three (57 SVES plus 16 IVES) episodes fulfilled VRH criteria; only one SVES episode did not. Median (IQR) post-VE MABP value increased from 30 (28–34) mmHg obtained during arterial hypotension to 42 (37–45) mmHg in these 73 VRH episodes ($p < 0.001$). Median (IQR) PVI value during arterial hypotension was 23 % (20–25 %), and post-VE PVI was 16 % (13–18 %) ($p < 0.001$) (Fig. 1). Median (IQR) percentage change in PVI was +31 % (+20 % to +41 %) from prehypotension PVI to during-hypotension PVI [(hypo-PVI − pre-PVI)/hypo-PVI] and −44 % (−64 % to −29 %) from during-hypotension PVI to post-VE PVI [(post-PVI − hypo-PVI)/post-PVI], respectively. Median (IQR) post-VE PI value increased from 0.9 (0.7–1.6) obtained during arterial hypotension to 1.3 (0.9–2.1) in these 73 VRH episodes ($p < 0.001$).

Median (IQR) heart rate (HR) before and during arterial hypotension were 155 (134–168) beats/min and 163 (147–178) beats/min; HR after VE decreased to 153 (136–167) beats/min (pre-hypotension HR vs. during-hypotension HR and during-hypotension HR vs. post-VE HR, $p < 0.001$). Sixty-three of 73 mean during-hypotension PVI values were >18 %, the initially defined upper limit of the reference range, resulting in an 86 % sensitivity for VRH with an exact 95 % CI of 76–93 %. Whereas

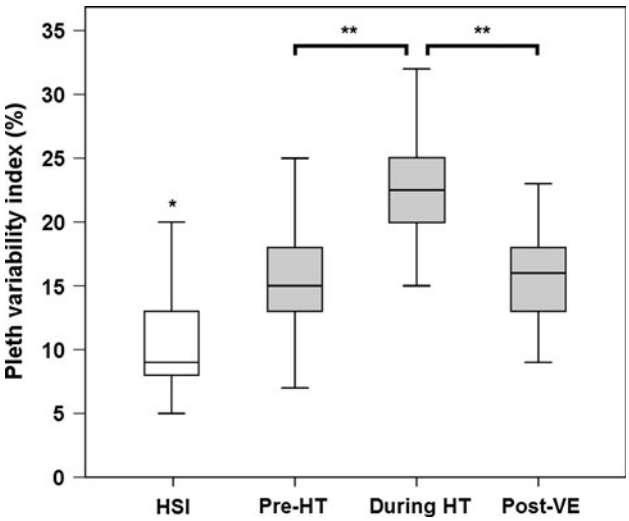

Fig. 1 Comparison of pleth variability index (PVI) values before hypotension (pre-HT PVI), during hypotension (HT), and after volume expansion (post-VE PVI) in 73 episodes with volume-responsive hypotension. To compare PVI values of infants needing volume expansion (VE), the plot of PVI values of hemodynamically stable infants (HSI) is also demonstrated. There was a statistically significant difference between median (IQR) prehypotension PVI [15 % (13–18 %)] and PVI during arterial hypotension [23 % (20–25 %)] and between PVI during arterial hypotension and post-VE PVI [16 % (13–18 %)] (*$p < 0.001$ for hemodynamically stable infants (HSI) vs. pre-HT PVI, HSI vs. PVI during HT, and HSI vs. post-VE PVI, **$p < 0.001$)

post-VE PVI decreased to ≤18 %, i.e., returned into the reference range, in 45 (79 %) of 57 SVES episodes with adequate initial VE, intermediate PVI values after clinically insufficient VE decreased to ≤18 % in only 13 (50 %) of 26 IVES episodes ($p < 0.001$). During the 26 episodes with apparent IVES, the following volumes were administered: 14 episodes with >10 ml/kg crystalloid, three episodes with 5–10 ml/kg colloid, and nine episodes with >10 ml/kg colloid. Median (IQR) intermediate PVI value in IVES episodes was significantly higher than

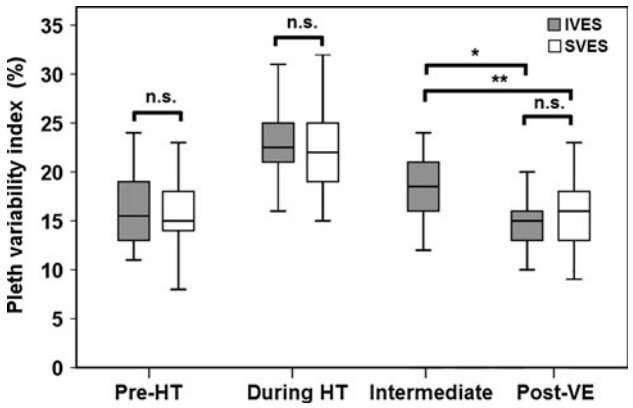

Fig. 2 Comparison of pleth variability index (PVI) values between insufficient volume expansion size (IVES) episodes ($n = 16$) and sufficient volume expansion size (SVES) episodes ($n = 57$). Intermediate PVI shows mean values during the 3-min interval after completion of the 26 VE in IVES episodes, which were followed by additional VE within 3 min (*$p = 0.004$; **$p = 0.003$)

post-VE PVI in SVES [18 % (16–21 %)] vs. 16 % (13–18 %), $p = 0.003$, respectively) (Fig. 2).

Discussion

Our study suggests that PVI, a parameter that can be determined continuously and noninvasively, may serve as a valid predictor of volume responsiveness in mechanically ventilated newborn infants during surgery. The ultimate goal of perioperative fluid therapy is to provide basal metabolic requirements and replace losses from the surgical field to maintain normal cardiovascular function. Total body water comprises as much as 85 % of body weight in premature infants and 75 % in full-term newborns, compared with only 60 % in adults. Extracellular fluid (including third space) represents 50 % of body weight in premature infants and 45 % in full-term newborns, compared with only 20 % in adults [18]. The perioperative state of hydration and third-space losses in newborn infants depend on maturity and type of surgical procedure. Third-space losses may vary from 1 ml/kg per hour for a minor surgical procedure, such as hernia repair, to as much as 15–20 ml/kg per hour for major abdominal procedures of gastroschisis and omphalocele, or even up to 50 ml/kg per hour for surgery of necrotising enterocolitis in premature infants [19]. Despite the near universal practice of administering fluid boluses to hypotensive infants, it should be considered that the cardiovascular system in neonates is immature compared with that of adults. In addition to alterations in cardiac loading conditions at delivery, contractility, myocardial function, and histological structure of the ventricular myocardium change after birth. Even at rest, the neonate is functioning near full capacity, with reduced reserve in contractility, preload, or afterload. As the newborn heart has less ability to adapt to additional acute pressure (afterload) or volume (preload) stresses, excessive volume administration is associated with increased morbidity and mortality, particularly from pulmonary hemorrhage in extremely-low-birthweight infants [20, 21]. This data stresses the need for continuous monitoring of fluid status and timely and adequate replacement of fluids in this high-risk newborn population.

Cannesson et al. [22] first described that PVI as an automatically and continuously calculated parameter strongly correlates to ΔPOP and is useful to predict fluid responsiveness in mechanically ventilated patients [11]. They and others showed that PVI can detect hemodynamic changes and predict cardiocirculatory response to volume loading in a hemodynamically stable setting during surgery [12]. Our study is the first report to demonstrate the ability of PVI to predict fluid responsiveness in newborn infants undergoing surgery. Cannesson et al. [11] demonstrated that the cutoff value to distinguish responders from non-responders to intravascular VE was a PVI > 14 %. This was confirmed later by Forget et al. [23]. Recently, Latini et al. [24] evaluated the reference range of PVI in newborns. However, those studies included only spontaneously breathing term newborns. In our study, we defined PVI cutoff value by the 95th percentile of all PVI values from five mechanically ventilated newborn infants who did not receive any VE during surgery. Different effects of vascular compliance, heart–lung interaction, and location of the probe between neonates in our study ventilated with relatively high positive end-expiratory pressure (PEEP) and low tidal volumes, compared with the adults studied by Cannesson et al. ventilated with low PEEP and relatively high tidal volumes, may contribute to this difference in PVI cutoff. In our study, in 63 of 73 VRH episodes, during-hypotension PVI values were >18 % (86 % sensitivity for VRH).

It should be emphasized that, compared with adult studies, our study population has major anatomical and physiological differences, which may necessitate additional attention during PVI monitoring and results analysis. As known, pulse oximetry waveform relies on the two components (AC and DC) of light absorption. DC is determined by light absorption by bone, tissue, pigments, nonpulsatile blood, and skin. AC is proportional to the pulsatile absorption, which is primarily determined by arterialized blood. PI is defined as the ratio between constant and pulsatile absorption, reflecting the amplitude of the plethysmographic waveform [25]. As the resulting waveform contains a complex mixture of influences from the cardiovascular, autonomic, and respiratory systems on peripheral circulation, the choice of probe site can have a significant impact on strength of the respiratory signal

detected within the plethysmographic waveform [26]. The previously published studies focusing on ΔPOP and PVI were performed in adults and measured the pulse oximetry plethysmographic waveform at the finger, ear, or forehead. In our study, however, PVI was recorded in newborn infants with the probe placed at the hand or foot. Furthermore, tidal volume applied during mechanical ventilation influences PVI performance to detect cardiovascular instability [27], and the newborn infants were ventilated with smaller tidal volumes (in general, 4–6 ml/kg) than were the adult patients previously studied. Finally, previous studies determined PVI in patients in stable condition (suggesting optimal pulse oximetry readings) [22, 23, 28, 29]. However, in newborn surgery, pulse oximetry readings are frequently compromised because of poor peripheral perfusion [30] and by the surgeons almost inevitably touching the extremity where the pulse oximetry probe is placed. Results of this pilot study, including the cutoff value for the PVI described herein, therefore have to be considered preliminary.

A limitation of the study is that we were not able to compare PVI readings during VRH and volume nonresponsive hypotension because of the lack of episodes with volume-nonresponsive hypotension. We therefore are unable to estimate the discriminatory ability of PVI and the specificity at the proposed cutoff of >18 %. Another limitation is that the attending physician indicating VE administration was not blinded to the PVI reading. Because pulse oximetry readings are often compromised during neonatal surgery, we believed it would be advantageous for our patients if the attending clinicians had the chance to also rely on the SpO_2 reading of the additional pulse oximeter. In retrospect, it is unlikely that the PVI changed the clinician's decisions because: (1) the highest PVI values were recorded after initiation of VE(probably due to the long averaging time); (2) 5 % of PVI readings above the trigger threshold of 18 % in the five patients clinically considered to be hemodynamically stable did not result in VE administration; (3) clinicians were not familiar with the PVI and did not know a reference range.

Another study limitation is that because predominantly term and near-term newborn infants only were enrolled and all infants were mechanically ventilated, results cannot be extrapolated to extremely preterm infants or infants with spontaneous respiration. Furthermore, the effect of a shorter averaging time for PVI needs to be determined in the setting of newborn surgery because of the dramatic cardiovascular instability and the extremely fast changes in blood pressure and perfusion observed in these infants. A further limitation is that episodes of intermittent hypotension that did not trigger VE were not recorded. Moreover, we did not evaluate the effect of inotropes and vasoconstrictors on PVI because episodes with simultaneous changes in inotropic support were not recorded. Also, the study design does not permit differentiation as to whether blood pressure increased after VE because of a true need for VE or because of some other factor, e.g., impaired venous return by compression of the vena cava being removed at the same time. Furthermore, the criterion chosen to define response to VE (i.e., increase in MABP by >10 %) was selected arbitrarily although a priori.

Because repeated VE episodes in the same patients were reported in order to increase the number of observations, and thus may not be considered strictly independent observations, we recalculated median (IQR) prehypotension PVI [14 %(13–18 %)], PVI during hypotension [24 % (19–25 %)], and post-VE PVI [15 % (14–18 %)] for only the first VE episode in the 24 infants included, with nearly identical results ($p < 0.001$ for prehypotension PVI vs. PVI during hypotension; and PVI during hypotension vs. post-VE PVI).

In conclusion, our pilot study suggests that PVI may predict VRH in mechanically ventilated newborn infants during surgery, but it is too early to give any recommendation for PVI-guided volume therapy in this very vulnerable population. However, a noninvasive parameter that could guide volume administration under the difficult condition of neonatal surgery would be extremely helpful. Future studies may need to validate PVI against indices of cerebral oxygenation, blood-gas analyses, lack of acidosis, and echo-Doppler hemodynamic parameters.

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Conflict of interest Masimo provided pulse oximetry and sensors. Since the conduct and completion of the study reported herein, Axel Franz has collected clinical data for Masimo and has been granted equipment for a large clinical study by Masimo. All other authors have no conflict of interest.

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