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RESEARCH REPORT

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The predictive value of the Pleth Variability Index on fluid responsiveness in spontaneously breathing anaesthetized children—A prospective observational study

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Abstract

Background: In children, the preoperative hydration status is an important part of the overall clinical assessment. The assumed preoperative fluid deficit is often routinely replaced during induction without knowing the child's actual fluid status.

Aim: We investigated the predictive value of the Pleth Variability Index as a measure of fluid responsiveness in spontaneously breathing anesthetized children.

Methods: Pleth Variability Index, stroke volume and Cardiac Index, measured by electrovelocimetry, mean blood pressure, and heart rate were recorded during anesthesia induction in 50 pediatric patients <6 years. Baseline values were compared to values recorded after administration of 10 mL/kg of Ringer's lactate and during two passive leg raising tests (before and after fluid administration). Fluid responsiveness was defined as an increase of ≥10% in stroke volume.

Results: Only in fluid responsive patients, Pleth Variability Index values were higher before fluid administration than thereafter (21.4 ± 5.9% vs 15.0 ± 9.4%, 95% CI of difference 1.1 to 11.8%, $P = .02$). Pleth Variability Index values at baseline were higher in fluid responders (21.4 ± 5.9%) than in fluid nonresponders (15.3 ± 7.7%), 95% CI of difference 1.6 to 10.6%, $P = .009$. The area under the receiver operating curve indicating fluid responsiveness was 0.781 (95% CI 0.623 to 0.896, $P = .0002$), with the highest sensitivity (82%) and specificity (70%) at a Pleth Variability Index of >15% (Positive predictive value 2.71 (95% CI: 1.4 to 5.2)). Only in fluid responders, the Pleth Variability Index decreased during passive leg raising, while stroke volume increased.

Conclusions: The Pleth Variability Index may be of additional value to predict fluid responsiveness in spontaneously breathing anesthetized children. A significant overlap in baseline Pleth Variability Index values between fluid responsive and nonfluid responsive patients does not allow a reliable recommendation as to a cut off value.

KEYWORDS

general anesthesia, non-invasive, neonate, infant

1 | INTRODUCTION

Maintaining an adequate fluid status is essential to the safe conduct of anesthesia. Firstly, the challenging task to properly assess the patient's intravascular volume status upon arrival at the operating room has to be mastered. In pediatric anesthesia, it is common practice to assess this hydration status as a part of the overall clinical impression of the child's condition. This approach is usually sufficient to detect clinically relevant forms of dehydration or volume overload which require an immediate intervention, preferably prior to the induction of anesthesia. Though the majority of our elective pediatric surgical patients can be considered being no more than relatively dehydrated with no clinical signs of volume depletion, induction of anesthesia and the resulting reduction of vasotension together with some degree of negative inotropic anesthetic drug effect may result in reduced organ perfusion. To preserve appropriate organ perfusion, it is common practice in many pediatric centers to apply a moderate pre-emptive fluid resuscitation during anesthesia induction, regardless of the child's actual fluid status.

The principle of fluid responsiveness prediction helps distinguish between patients that benefit from a pre-emptive infusion of balanced crystalloid fluids and those that are not fluid depleted.

The respiratory variability of plethysmographically measured arterial pulse pressure variation, serving as a surrogate parameter for stroke volume has been shown to be predictive of the degree of biventricular preload responsiveness and hemodynamic fluid responsiveness in mechanically ventilated adult patients.[1,2]

The plethysmography-derived Pleth Variability Index (PVI, Masimo Corporation) has been investigated as a predictor of fluid responsiveness in mechanically ventilated anaesthetized children. The majority of these studies came with positive[3-6] results, though there were also papers reporting negative[7] and inconclusive[8] results.

Whether or not the PVI can help assess the volume status of spontaneously breathing anesthetized children remains subject of debate. From a theoretical point of view, mechanical ventilation with a regular variation in airway pressure amplitude, constant respiratory frequency, and a fixed tidal volume may be considered essential to evoke predictable cardiopulmonary interactions that allow to link pulse pressure variability with fluid responsiveness.[1,9] The currently available scientific literature on plethysmographic pulse pressure variation as a predictor of fluid responsiveness in spontaneously breathing adult patients and volunteers is sparse, and comes with inconclusive results.[9-11]

It is common practice in many pediatric centers to let children breathe spontaneously through a laryngeal mask during surgical procedures when intraoperative analgesia is provided by locoregional techniques. Unfortunately, we do not know yet whether the PVI provides reliable information regarding the fluid status in this particular patient group.

In this study, we prospectively investigated the performance of the PVI as a predictor of fluid responsiveness in spontaneously breathing anesthetized children. Fluid responsiveness was defined as an increase in stroke volume of ≥10% after a fluid challenge with 10 mL/kg of Ringer's lactate.

What is already known about the topic

- At present there is no consensus among pediatric anesthesiologists as to the definition of fluid responsiveness and how to assess it.
- Plethysmographic assessment of arterial pulse pressure variation may have the potential to help predict fluid responsiveness in mechanically ventilated anaesthetized children.

What new information this study adds

- The plethysmography-derived Pleth Variability Index (PVI) may be of additional value to predict fluid responsiveness in spontaneously breathing anaesthetized children.
- A significant overlap in baseline PVI values between fluid responsive and nonfluid responsive patients does not allow the provision of a valid PVI cut off value indicating fluid responsiveness

2 | METHODS

This study was approved by the Medical Ethics Committee of Erasmus University Medical Center, Rotterdam, The Netherlands (Chairperson Prof. H. W. Tilanus), on November 29, 2019 (MEC-2019-0694). Parental written informed consent was obtained for all participating patients.

2.1 | Inclusion criteria

Patients up to six years of age scheduled for subumbilical surgery performed under combined general anesthesia (sevoflurane) and epidural analgesia (single shot caudal block) were eligible for inclusion.

2.2 | Exclusion criteria

Patients with a known allergy to sevoflurane, propofol or ropivacaine, an anticipated difficult airway scenario, or contraindications for caudal epidural analgesia were not considered eligible for inclusion.

The same accounts for conditions that interfere with the consistency of heart lung interactions, such as pressure support ventilation and cardiac arrhythmias.

Anesthesia protocol.

Patients received standard anesthetic treatment according to departmental standards:

Anesthesia induction was either performed using propofol 2-3 mg/kg or via facemask with sevoflurane in 50% O_2, starting with a fraction inspired of 8% until loss of consciousness, subsequently adjusted to an endtidal concentration of ≈4% until intravenous access was obtained and the airway secured with a laryngeal mask.

All patients received a caudal block with 1-1.2 mL/kg ropivacaine 0.2%. Prior to caudal epidural puncture, up to 0.1 μg/kg intravenous sufentanil was given at the discretion of the attending pediatric anesthesiologist.

In order to—at least partially—compensate for preoperative fluid depletion, 10 mL/kg of Ringer's lactate was infused over ≈10 min. during caudal block application.

Following departmental standards, patients breathed spontaneously throughout the surgical procedure at an endtidal sevoflurane concentration of ≈2.5%, with low (3-5 cm H_2O) positive end-expiratory pressure.

2.3 | Study-related data recordings

Standard anesthesia monitoring was applied using Dräger Infinity technology (Dräger) and Masimo SET® pulse oximetry (Masimo Corporation). Data were stored in our institutional electronic patient data management system.

Cardiac index (CI; l min·m^2) and stroke volume (SV; mL) were noninvasively measured using the electrovelocimetric ICON monitor (OsypkaMedical GmbH).

Narula et al[12] conducted a study in children with a variety of structural congenital heart defects and concluded that ICON provides a reliable noninvasive estimation of CO. In another pediatric study Altamirano-Diaz et al[13] found strong correlations for CO and SV measured simultaneously with ICON and transthoracic echocardiography, with the exception of obese patients, where electrovelocimetry tended to underestimate CO and SV.

A recent meta-analysis including a subgroup analysis of 11 pediatric studies, comparing cardiac output values derived from electrovelocimetry and transthoracic echocardiography (n = 9) and thermodilution (n = 2), found a random effects pooled bias of −0.02 L/min [95% CI −0.09 to 0.05 L/min], a limit of agreement of −1.22 to 1.18 L/min, and a mean percentage (MPE) error of 42.0%. Considering a pooled MPE of <30% as acceptable, the authors concluded that despite a low bias electrovelocimetry is unlikely to completely replace echocardiography or thermodilution, but seems to be applicable as a trend monitor capable of measuring acute changes in cardiac output in both children and adults.[14]

2.4 | Data collection

Pleth Variability Index (PVI), Perfusion Index (PI), Cardiac Index (CI), stroke volume (SV), heart rate, and noninvasive blood pressure were specifically recorded at the following time points for subsequent analysis:

T1: Baseline dataset, after laryngeal airway placement.

T2: Passive leg raising test before fluid application.

T3: Immediately after infusion of 10 mL/kg of Ringer's lactate.

T4: Passive leg raising test immediately after T3, prior to the start of surgery.

The pulse oximeter was attached to a finger in all patients, because lower extremity pulse oximetry might have come with the risk of high PI values due to the possibility of very early onset vasodilatory effects of epidural analgesia.

2.5 | Perfusion Index (PI) and Pleth Variability Index (PVI)

Though this study was designed to investigate the Pleth Variability Index (PVI), for a better understanding of the underlying principle it may help to introduce the Perfusion Index (PI) first:

The *Perfusion Index (PI)* is a relative assessment of the strength of a pulse, measured by a pulse oximeter (Masimo SET® pulse oximetry, Masimo Corporation). The PI is a measure of the ratio of pulsatile and nonpulsatile detected signals; as such it corresponds to the pulsatile and nonpulsatile amounts of blood. The PI is presented as percentages from 0.2 to 20, with high PI values indicating high pulse-detected signals, and low PI values indicating low pulse-detected signals. The plethysmograph is also affected by the respiratory cycle; physiological respiratory changes in cardiac preload lead to variations of the amount of blood under the pulse oximeter resulting in an inspiratory/expiratory swing of the waveform (PI_{Max} and PI_{Min}).

The *Pleth Variability Index (PVI)* is an expression of that respiratory-driven variation of the PI. It is calculated according to the equation

$$PVI = \frac{PI_{Max} - PI_{Min}}{PI_{Max}} x100\%$$

The PVI given as a percentage value is positively correlated with the variability of the PI over a respiratory cycle. The higher the variability the higher the likelihood of fluid responsiveness.

As eloquently explained by Guerin et al,[1] adult patient data have shown that regular variation of intrathoracic pressure, as originated from mechanical ventilation, is necessary to relate variation in stroke volume to preload dependency. Even breathing efforts under mechanical ventilation, not to mention spontaneous breathing, result in irregular variation in intrathoracic pressure, both in rate and amplitude.

It remains to be determined whether these requirements must also be met in young children.

2.6 | Passive leg raising test

Passive leg raising (PLR) has been used for decades to predict preload dependence of cardiac output. Raising the patient's legs to

45° mimics the effects of volume expansion. In case of preload dependency of the heart, the resulting increased venous return will lead to an increase in cardiac output.

Lukito et al[15] applied a PLR test in pediatric ICU patients, defining fluid responsiveness as an increase in cardiac output of ≥10% after a fluid challenge of 10 mL/kg of NaCl 0.9%, administered over 15 minutes.

In their 2016 meta-analysis (adult patient data only), Monnet et al[16] concluded that a PLR test is a valid predictor of fluid responsiveness, with a better accuracy when hemodynamic effects are described by changes in cardiac output compared to their assessment by arterial pulse pressure.

2.7 | Statistics and sample size

Continuous data were tested for normality using a Kolmogorov-Smirnov test and visual inspection of the data plot. Subsequent analyses were performed accordingly, and data presented as either mean ± SD or median [IQR] as appropriate.

A paired t test was performed to compare PVI, PI, SV, CI, MAP, and HR at baseline and after the administration of 10 mL/kg of Ringer's lactate. For this particular analysis, patients were divided in two groups: Following a definition suggested by Lukito et al,[15] fluid responsiveness (FR_{pos}) was defined as an increase in baseline SV of at least 10% after fluid administration, whereas less than 10% increase in SV was defined as lack of fluid responsiveness (FR_{neg}).

A receiver operating curve (ROC) analysis was performed to investigate the performance of the PVI as a predictor of fluid responsiveness. Positive Likelihood Ratios (LR+) for various PVI cut off values were calculated. The positive Likelihood Ratio can mathematically be expressed as [True-positive rate/False-positive rate = Sensitivity/ (100-Specificity)].

An unpaired *t* test was performed to compare the PVI at baseline between patient groups FR_{pos} and FR_{neg}.

A repeated measures mixed model analysis using the same set of parameters was performed to compare the effects of a passive leg raising test before and after fluid administration to baseline conditions.

Due to the lack of scientifically sound data, it was not possible to perform a valid sample size calculation. We assumed that data collected in 50 patients would provide us with sufficient information to draw some initial tentative conclusions as to the capability of the PVI to predict fluid responsiveness in spontaneous breathing anesthetized children.

Statistical analyses were performed using Prism for macOS (version 8.4.3, GraphPad Software) and MedCalc (version 19.3.1, MedCalc Software Ltd). *P* values <.05 were considered significant.

2.8 | RESULTS

Between December 2019 and February 2020, 50 patients were enrolled in this study. Data from ten patients had to be secondarily excluded from analysis; in seven children the fluid bolus was administered too slowly, two patients received pressure support ventilation, and in one patient equipment failure resulted in loss of PVI data. Characteristics of the remaining 40 patients available for data-analysis are presented in Table 1.

In 17 children, fluid administration resulted in a ≥10% increase in SV, and these patients were classified as fluid responsive (FR_{pos}). Twenty three patients showed an increase of less than 10% in SV after fluid administration, and they were classified as not fluid responsive (FR_{neg}).

A receiver operating curve (ROC) analysis, investigating the performance of the PVI as a predictor of fluid responsiveness, revealed an area under the ROC curve of 0.781 (95% CI: 0.623 to 0.896, $P = .0002$). More detailed information is given in Table 2 and Figure 1.

TABLE 1 Patient characteristics

	FR_{pos}	FR_{neg}	*P* value
Age (mo)	7 [6 to 29]	10 [8 to 17]	.995
Female/Male (n)	1/ 16	0/ 23	-
Weight (kg)	10.5 [7.5 to 14.3]	10 [8.6 to 11.5]	.866
Height (cm)	85 [69 to 117]	80 [70 to 88]	.519
Mask Induction/ iv induction (n)	15/ 2	17 /3	-
Opioid before caudal block (n)	15	20	-
Surgical procedure	(n)		
Circumcision	1		
Cystoscopy	5		
Inguinal hernia repair	6		
Hypospadia correction	10		
Orchidopexy	18		

Note: Patient data (except Female/Male) are given as median [IQR].

TABLE 2 Receiver operating curve (ROC) analysis

PVI Cut off	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)
AUC 0.781 (SE 0.07), 95% CI 0.623 to 0.896; P = .0002			
> 11	100 (81 to 100) %	30 (13 to 53) %	1.44 (1.1-1.9)
≥ 38	0 (0 to 20) %	100 (85 to 100) %	-
> 15	82 (57 to 96) %	70 (47 to 87) %	2.71 (1.4 to 5.2)

Note: Youden Index 0.519 (95% CI 0.229 to 0.696).

Associated Criterion (PVI) >15 (95% CI > 11 to > 20).

Receiver Operating Curve (ROC) analyses for Pleth Variability Index (PVI) at baseline as a predictor of fluid responsiveness. PVI cut off values and positive Likelihood Ratios (LR+), both with 95% confidence intervals, correspond to either 100% sensitivity, 100% specificity, and the optimal combination of sensitivity and specificity (Youden Index).

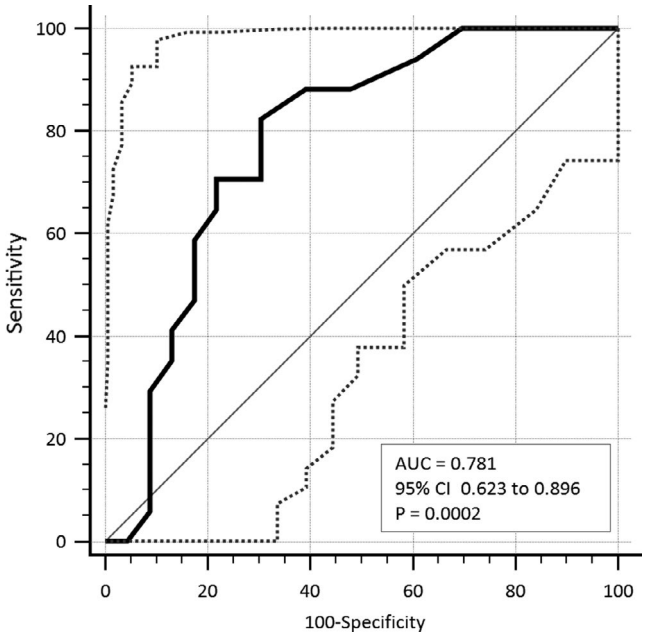

FIGURE 1 Receiver operating curve (ROC). ROC curve with 95% confidence bounds indicating the power of the Pleth Variability Index (PVI) to distinguish between fluid responsiveness and lack of fluid responsiveness

In group FR_{pos}, PVI values were higher at baseline than after fluid administration (21.4 ± 5.9 vs 15.0 ± 9.4%, 95% CI of difference 1.1% to 11.8%, $P = .02$). In group FR_{neg}, there was no evidence of a difference between PVI values at baseline and after fluid administration (15.3 ± 7.7 vs 12.4 ± 5.3%, 95% CI of difference −1.0% to 6.8%, $P = .136$). There was also no evidence of a difference in PI, mean blood pressure, and heart rate between baseline and postfluid administration in either study group; for further information please see Figure 2. Baseline PVI values in group FR_{pos} were higher than in group FR_{neg} (21.4 ± 5.9% vs 15.3 ± 7.7%, 95% CI of difference 1.6% to 10.6%, $P = .009$).

In study group FR_{pos}, the PVI during the PLR tests before and after fluid administration was lower than baseline, while SV and CI increased. In study group FR_{neg}, we found no evidence of a change in hemodynamic parameters during the two PLR tests; more detailed information is available in Table 3.

Endtidal sevoflurane concentrations were comparable between study groups at baseline (FR_{pos} 2.7 ± 1.1% vs FR_{neg} 2.8 ± 0.9%, 95% CI of difference −0.66 to 0.59%, $P = .905$) and after fluid administration (FR_{pos} 2.5 ± 0.4% vs FR_{neg} 2.5 ± 0.4%, 95% CI of difference −0.22% to 0.3%, $P = .735$).

3 | DISCUSSION

In this study performed in spontaneously breathing anesthetized children baseline, PVI values in fluid responsive patients (FR_{pos}) were higher than in those not responding to a crystalloid fluid challenge(FR_{neg}). In FR_{pos} patients, PVI values significantly declined after fluid administration, while this was not observed in FR_{neg} patients. Our findings allow us to tentatively conclude that the PVI might be of some value as predictor of fluid responsiveness in anesthetized spontaneously breathing young children.

Receiver operating curve analysis revealed an area under the ROC curve of 0.781 (95% CI: 0.623 to 0.896, $P = .0002$). Youden's J Index (Sensitivity + Specificity −1) was 0.519 and the associated PVI value to predict fluid responsiveness was >15%, with a sensitivity of 82% a specificity of 70%, and a positive predictive value of 2.71 (95% CI: 1.4 to 5.2). Lower threshold values result in a decrease in specificity and an increase in sensitivity, whereas higher threshold values cause opposite changes (see Table 2). Though we would like to have both sensitivity and specificity close to 100%, PVI thresholds with either a high specificity or a high sensitivity may be of some clinical value, depending on patient characteristics/pathology. In a child that is prone to cardiac failure due to volume overload (ie, with a hemodynamically relevant ventricular septum defect), it might be wise to choose a threshold with a high specificity, whereas in a volume dependent child (ie, a Fontan circulation) the decision to give a fluid bolus should preferably be made using a threshold with a high sensitivity.

3.1 | Pediatric PVI studies

Several pediatric studies investigating the PVI as a predictor of fluid responsiveness in mechanically ventilated anesthetized children have been published during the last decade.[3-8]

In these studies, fluid challenges were performed with both colloids and crystalloids, volumes ranged from 10 to 20 mL/kg, and there was no consistency in the definition of fluid responsiveness. As a consequence of a significant diversity in study design, the reported PVI thresholds for fluid responsiveness ranged from >11% to >18%.

It is obvious that, due to the diversity in interventions and outcome variables, the pediatric studies investigating the predictive value of the PVI regarding fluid responsiveness published thus far

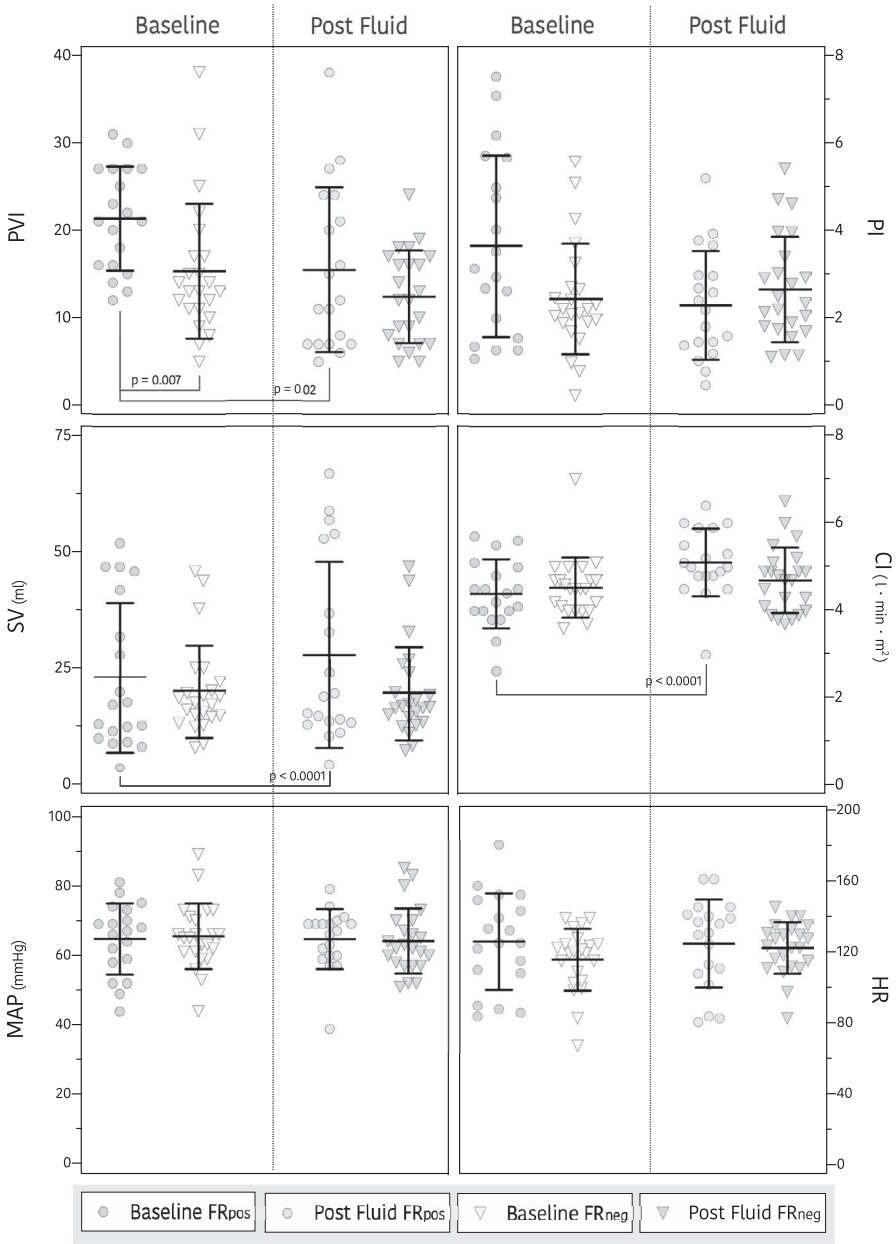

FIGURE 2 Effects of fluid challenge on PVI, PI, and hemodynamic parameters. Individual values, bars represent mean values, and whiskers represent SD. FRneg, non fluid responsive patients; FRpos, fluid responsive patients; HR, heart rate; MAP = mean arterial blood pressure; PI, perfusion Index; PVI, Pleth Variability Index; SV, stroke volume

are almost incomparable to each other and our study. Consensus among future researchers in this field, particularly regarding outcome parameters, would certainly be useful.

3.2 | Pleth Variability Index in spontaneous breathing patients

There is an ongoing debate regarding the applicability of the PVI in spontaneously breathing patients. Based on cardiorespiratory physiology purists recommend the use of PVI only in mechanically ventilated patients. However, our data provide initial evidence that the PVI might be of some value in spontaneously breathing anesthetized young children.

In our study, data collection took place after induction of general anesthesia. Both sevoflurane[17] and propofol[18] have dose-dependent vasodilatory and negative inotropic properties, particularly in neonates and infants. Minor negative effects of anesthetic drugs on vasotension may thus be assumed.

While we can at least partly account anesthetic drug effects (vasodilation) for some of our findings, it is crucial to acknowledge that we collected data under no-touch conditions during the pre-incision period exclusively. Patients showed a stable regular breathing pattern, what might as well have contributed to our findings.

3.3 | Passive Leg Raising (PLR) test and fluid responsiveness

A PLR test can best be described as a reversible pseudo-volume challenge, as venous blood from the lower extremities is translocated to the upper body.

TABLE 3 Passive leg raising (PLR) tests and hemodynamic variables

		Baseline vs PLR 1		Baseline vs PLR 2	
Group	Parameter	Mean diff.(SE)	*P*	Mean diff.(SE)	*P*
FR_{pos}	PVI	4.9 (1.1)	.0008	5.7 (2.4)	.029
	PI	−0.5 (0.3)	.113	−1.2 (0.5)	.063
	SV	−1.0 (0.4)	.012	−4.2 (1.2)	.006
	CI	−0.3 (0.1)	.006	−0.6 (0.1)	.0008
	MAP	0.3 (2.2)	.896	5.1 (2.0)	.049
	HR	−0.8 (2.8)	.931	1.3 (3.8)	.931
FR_{neg}	PVI	2.9 (1.9)	.253	0.5 (1.9)	.805
	PI	−0.5 (0.3)	.289	−0.4 (0.3)	.289
	SV	−0.1 (0.2)	.756	0.3 (0.3)	.576
	CI	0 (0)	.381	-0.2 (0.1)	.381
	MAP	0.7 (1.8)	.687	4.2 (1.9)	.073
	HR	−1.8 (1.6)	0.262	-4.7 (2.0)	.047

Note: Repeated measures mixed model analysis comparing parameters PVI, PI, SV (mL), CI (L/min m^2), MAP (mm Hg), and HR measured at baseline, during a passive leg raising test prior to (PLR 1) and after (PLR 2) fluid administration.

Lukito et al[15] applied a PLR test in pediatric ICU patients using a setting that was comparable to ours, defining fluid responsiveness as an increase in cardiac output of ≥10% after a fluid challenge of 10 mL/kg of NaCl 0.9%, administered over 15 minutes. In adult subjects, combining a PLR test and the PVI has been shown to improve the validity of the obtained information regarding the prediction of fluid responsiveness under spontaneous breathing conditions.[9-11]

We applied two PLR tests and found significant effects of PLR on PVI, SV, and CI both before and after fluid administration in the FRpos patient group, and no effect in the FRneg group (see Table 3).

The following new question arises: If a drop in PVI values during a PLR test is reliably associated with a rise in SV/CI, do we still need the advanced technology of cardiac output monitors to predict fluid responsiveness? This question is of significant practical importance, as many hospitals have the PVI incorporated in their standard monitoring while very few have noninvasive cardiac output monitors available. PVI changes during a PLR test may be an alternative approach to define a PVI cut off value indicating fluid responsiveness, not necessarily as an absolute number but probably as a percentage of change compared to baseline. Large-scale trials would be necessary to answer this question.

3.4 | Transferability of findings to the intraoperative period

As already mentioned, our study took place in the pre-incision period. None of the children presented with clinical signs of severe volume depletion, and no noxious stimulation was applied during data collection. We are aware that this situation is fundamentally different from the intraoperative setting, where noxious stimulation may affect the breathing pattern and volume shifts can interfere with plethysmography. We therefore consider it inappropriate to draw conclusions regarding the applicability of the PVI as a predictor of intraoperative fluid/volume responsiveness. The same accounts for seriously ill children undergoing emergency surgery.

Given the promising results of this study, further research investigating the validity of the PVI as a measure of the intraoperative volume status in anesthetized children either breathing spontaneously or on pressure support ventilation certainly makes sense.

4 | CONCLUSIONS

The PVI may be of additional value to predict fluid responsiveness in spontaneously breathing anesthetized children. This tentative conclusion applies only to the replacement of pre-anesthetic fluid deficits using Ringer's lactate during pre-incision period of the anesthetic. Due to a significant overlap in baseline PVI values between fluid responsive and nonfluid responsive patients, our results do not allow a reliable recommendation as to a PVI cut off value indicating fluid responsiveness under spontaneous breathing conditions.

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