Original Article

Dynamic variables predict fluid responsiveness in pre-school and school children undergoing neurosurgery: a prospective observational study

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Background: The evidence that plethysmographic variability index (PVI), pulse pressure variation (PPV), FloTrac/Vigileo-derived stroke volume variation (SVV), and Ea_{dyn} (dynamic arterial elastance) predict fluid responsiveness in children is limited by conflicting results. We aim to evaluate their accuracy and reliability to predict fluid responsiveness after induction in children aged 4–9 years undergoing major neurosurgery.

Methods: Children aged 4–9 years undergoing intracranial epileptic foci excision were enrolled. After the induction of anesthesia, fluid loading with 10 mL/kg of Ringer's solution over 10 min was administered before surgical incision. PVI, PPV, SVV, and Ea_{dyn} were measured before and within 5 min after fluid loading. Respiratory variation in aortic blood flow peak velocity (ΔVpeak) >15% at baseline, measured using transthoracic echocardiography, identified fluid "responders". The abilities of dynamic variables to predict an increase in mean arterial pressure (MAP) of >10% following fluid loading were also assessed.

Results: Fourteen (31.8%) of forty-four patients were responders defined by a baseline ΔVpeak >15%. Before fluid loading, only the PVI value was significantly different between R and NR (P=0.017). Baseline PVI showed fair diagnostic accuracy for fluid responsiveness, with an area under the curve (AUROC) of 0.735 and the cutoff value of 13%. The R group showed a significantly greater absolute change in PPV and SVV after fluid loading from baseline compared with the NR group (P=0.021 and 0.040, respectively). The absolute change in the PPV and SVV values from baseline was greater in R than those in NR (P=0.021 and 0.040, respectively). Twenty (45.5%) showed a MAP increase of >10% following fluid loading and were defined as responders. Baseline ΔVpeak and SVV showed fair predictive values for a MAP increase of >10% (AUROC =0.758 and 0.715, respectively).

Conclusions: PVI at baseline showed fair reliability to predict fluid responsiveness after anesthesia induction in mechanically ventilated children aged 4–9 years undergoing neurosurgery. Baseline ΔVpeak and SVV were fairly predictive for an increase in MAP following fluid loading.

Keywords: Children; plethysmographic variability index; pulse pressure variation; stroke volume variation; fluid responsiveness

Submitted Jun 17, 2021. Accepted for publication Aug 25, 2021.
doi: 10.21037/tp-21-281
View this article at: https://dx.doi.org/10.21037/tp-21-281

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Introduction

Judicious intravascular fluid management to achieve optimum cardiac performance is one of the most important hemodynamic goals in pediatric patients, especially in young children undergoing major surgery. Decreased intravascular volume is common in children undergoing neurosurgery because of preoperative fasting, the vasodilatory effects of anesthetics, and significant blood loss. The response rate to blinded volume expansion ranged from 45% to 69% (1). Excess fluid can increase cerebral edema following surgery-related disruption of the blood-brain barrier, and is associated with worse perioperative outcomes (2,3).

Optimally, preload variables should be accurate, continuous, noninvasive, and operator-independent. Dynamic preload variables are those that reflect the cyclical changes in left ventricle stroke volume (SV) induced by positive pressure ventilation. Their values are higher in hypovolemia, when the heart is functioning at the steep portion of the Frank Starling curve. Respiratory variation in aortic blood flow peak velocity (ΔVpeak), pulse pressure variation (PPV), stroke volume variation (SVV), plethysmographic variability index (PVI), dynamic elastance (Ea_{dyn}), and respiratory variation in inferior vena cava diameter have been proposed as superior predictors of fluid responsiveness (a surrogate of hypovolemia) in adults compared with static variables in several systematic reviews and meta-analyses (4-8). Children differ from adults in terms of cardiac performance, arterial compliance, chest wall and lung compliance. ΔVpeak has been confirmed as the only dynamic parameter that consistently predicts the responders to fluid loading in children in various clinical settings (1,9-12). However, the lack of continuity and expert clinicians in echocardiography decreases its utility in routine clinical practice (13).

In contrast to ΔVpeak, the evidence that continuous dynamic variables predict fluid responsiveness in children is limited with contradicting results (9,14,15). The predictive reliability of SVV extracted from central arterial contour analysis in children has yet to be determined (15). The FloTrac/Vigileo hemodynamic monitoring system (Edwards Lifesciences, Irvine, CA, USA; Software Version 4.02), which is based on arterial pulse contour analysis, refers to an autocalibration algorithm to obtain SV and SVV. Although several pediatric studies examined SVV's role in predicting fluid responsiveness, no previous studies have evaluated the predictive value of SVV measured using FloTrac/Vigileo in children with mechanical ventilation. PVI is a continuous dynamic variable that reflects periodic variation of the plethysmographic waveform caused by respiration. Clinical investigations into the ability of PVI to predict fluid responsiveness in pediatric populations have demonstrated inconsistent findings (9,15-19). Ea_{dyn} is considered as a functional parameter of arterial load (20), which has been less explored with regard to predicting fluid responsiveness in pediatric population (21).

Therefore, the objective of the present study was to evaluate the accuracy and reliability of SVV estimated by the FloTrac/Vigileo system to predict fluid responsiveness after induction in children aged 4–9 years undergoing major neurosurgery. The performances of PVI, PPV, and Ea_{dyn} as fluid responsiveness predictors were also assessed. We hypothesized that PVI, SVV, and Ea_{dyn} would accurately predict fluid responsiveness, defined by a baseline ΔVpeak >15% or an increase in mean arterial pressure (MAP) of >10% following fluid loading, while PPV would not. We present the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/tp-21-281).

Methods

This prospective observational study was conducted at Peking University First Hospital between August 2020 and March 2021. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of Peking University First Hospital, Beijing, China (Chairperson Prof YY Yu; ethical number: 2020-061). The study was registered prior to patient enrollment with the Chinese Clinical Trial Registry on May 25, 2020 (ChiCTR identifier: ChiCTR2000033245; principal investigator: Lin-Lin Song). And informed consent was taken from all patients' parent or legal guardian. Children aged 4–9 years scheduled for elective intracranial epileptogenic lesion excision under general anesthesia were approached for assessing the potential eligibility. Patients were excluded if they had congenital heart disease, cardiac arrhythmias, ventricular dysfunction (ejection fraction <50%), underlying pulmonary disease, increased intracranial pressure, or refusal of consent.

Anesthesia management

Anesthesia was induced with propofol 3 mg/kg, continuous infusion of remifentanil 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and sufentanil 0.1 μg/kg as needed. Mechanical ventilation was set in the

volume-controlled mode, a vital volume of 8 mL/kg of ideal body weight, an inspiratory:expiratory ratio of 1:2, positive end-expiratory pressure (PEEP) of 4 cmH_2O, and respiratory rate titrated to maintain normocapnia during surgery. Following the induction of anesthesia, a peripheral arterial catheter (22–24 G) was inserted in the radial artery, and the arterial line was connected to a FloTrac pressure transducer. The FloTrac transducer was subsequently connected to the Vigileo monitor and a BeneView T9 anesthesia monitor (Mindray Bio-Medical Electronics Corporation, Shenzhen, China), and was zeroed at the mid-axillary level to atmospheric pressure. The Masimo M-LNCS adhesive pulse oximeter sensor was attached to the thumb or index finger of one hand without an intravenous cannula and wrapped with an opaque cover to prevent outside light interference. The sensor was connected to the Masimo Radical-7 oximeter with PVI software (Masimo Corporation, Irvine, California, USA; Software Version 7.8). A forced-air warming system was applied to maintain body temperature >36 ℃.

Hemodynamic monitoring

ΔVpeak

The aortic blood flow waveform at the level of the aortic annulus or the left ventricular outflow tract was obtained using pulsed wave Doppler of transthoracic echocardiography (TTE) in the apical five-chamber view. All echocardiography acquisitions were performed by a single investigator, who had previously performed more than 100 TTE measurements. This investigator was blinded to all hemodynamic measurements using other monitoring devices during the experimental protocol. The echo cine-loops recording the aortic blood flow were saved for subsequent offline measurements of ΔVpeak. ΔVpeak was calculated as follows:

$$\Delta Vpeak\,(\%) = 100 \times \frac{Vpeak\ \max - Vpeak\ \min}{(Vpeak\ \max + Vpeak\ \min)/2} \quad [1]$$

where Vpeak max and Vpeak min were the maximum and minimum aortic blood flow peak velocities during a single respiratory cycle.

SVV

The FloTrac/Vigileo system comprises a dedicated FloTrac pressure transducer attached to the radial arterial line and the Vigileo monitor connecting the transducer. After the patients' age, height, weight and sex were entered, SV, cardiac output and SVV were continuously estimated and displayed. The SV was based on that pulse pressure is proportional to the standard deviation of arterial pulse pressure (PP_{SD}). The device calculates SV as

$$SV = PP_{SD} \times \mathrm{K} \quad [2]$$

where K is an autocalibration factor that incorporates the quantification of arterial compliance and vascular resistance based on waveform contour analysis and patient characteristics derived from a multivariate regression model. SVV was calculated as follows:

$$SVV\,(\%) = 100 \times \frac{SV\ \max - SV\ \min}{(SV\ \max + SV\ \min)/2} \quad [3]$$

where SVmin and SVmax were the minimum and maximum SVs over a time frame of 20 s.

That means,

$$SVV\,(\%) = 100 \times \frac{PP_{SD}\ \max \times K - PP_{SD}\ \min \times K}{(PP_{SD}\ \max \times K + PP_{SD}\ \min \times K)/2} \quad [4]$$

K is a constant during SVV calculation within one minute. Therefore,

$$SVV\,(\%) = 100 \times \frac{PP_{SD}\ \max - PP_{SD}\ \min}{(PP_{SD}\ \max + PP_{SD}\ \min)/2} \quad [5]$$

SVV calculated using FloTrac/Vigileo reflects PP_{SD}'s variation within 20 s. Although K is not validated in pediatric patients, leading to great errors in SV measurements using FloTrac/Vigileo, SVV is dependent on PP_{SD} max and PP_{SD} min within 20 s, which is not affected by inaccurate K. Therefore, SVV values in pediatric patients are as accurate as those in adult patients.

PPV

PPV was automatically calculated and displayed using the anesthesia monitor with the following equation:

$$PPV\,(\%) = 100 \times \frac{PP\ \max - PP\ \min}{(PP\ \max + PP\ \min)/2} \quad [6]$$

where PPmax and PPmin were the maximum and minimum pulse pressures over a time frame of 10 s according to the manufacturer's algorithm.

PVI

The Masimo Radical-7 oximeter measured pulse oxygen saturation, perfusion index (PI), and PVI noninvasively and continuously based on transcutaneous multiwavelength analysis of plethysmographic waveforms. The PI is the

ratio between the infrared pulsatile (alternating current) signal caused by pulsatile arterial flow and the infrared nonpulsatile (direct current) signal, which is affected by skin, nonpulsatile blood, and other tissues. The PVI was calculated as follows:

$$PVI(\%) = 100 \times \frac{PI\max - PI\min}{PI\max} \quad [7]$$

where PImin and PImax were the minimum and maximum PIs over a time frame of 2–3 min.

Ea_{dyn}

Ea_{dyn} is considered as a functional parameter of arterial load, which is calculated as PPV/SVV according to previous studies (20).

Experimental protocol and definition of fluid responder

After the induction of anesthesia, fluid loading was started during a hemodynamically stable phase before surgical incision. Fluid loading was conducted with 10 mL/kg of Ringer's lactate solution over 10 min, and then all variables (except for ΔVpeak) were measured before and within 5 min following fluid loading prior to surgical incision. ΔVpeak at baseline >15% identified fluid "responders" (R) and ΔVpeak ≤15% identified fluid "nonresponders" (NR). We chose a cutoff value of 15% based on the findings of previous studies, which indicated that this difference had clinical significance (10,15,22-24). The other definition of fluid responsiveness examined was an MAP increase of >10% following fluid loading. One anesthesiologist blinded to the echocardiographic measurement managed the status of the patients and the fluid loading protocol over the study period. The ventilator settings and all other therapeutics were unchanged.

Measurements

Offline measurement of ΔVpeak was performed by the TTE operator and a second echocardiography expert who were blinded to the patient data. The average of the measurements of ΔVpeak over three consecutive respiratory cycles by two investigators was used for statistical analysis. The following hemodynamic and respiratory parameters were collected: heart rate, systolic arterial pressure (SAP), MAP, SVV, PPV, PI, PVI, end-tidal CO_2, peak inspiratory pressure, and plateau pressure. The average of the three consecutive measurements taken at 1-min intervals before and after fluid loading were recorded for statistical analysis.

Sample size calculation

We assumed that the ratio of the numbers between the R and NR groups was 1:2.5 according to the pilot data from our institution. The sample size was determined by assuming that area under the receiver operating characteristic curve (AUROC) of a variable to predict fluid responsiveness was larger than 0.9, compared with the null hypothesis of having an AUROC of 0.5. A minimum of 42 patients with 12 responders and 30 nonresponders were required using a two-tailed *t*-test with an α-error of 0.05 and power of 0.9. To account for potential dropouts, 46 patients were enrolled.

Statistical analysis

Descriptive statistics are presented as the mean ± standard deviation (SD), median [interquartile range (IQR)], or counts and percentages where appropriate. Variables were compared before and after fluid loading using the paired *t*-test or Wilcoxon signed-rank test. The differences between responders and nonresponders at baseline and after fluid loading were evaluated using the Student's *t*-test or the Mann-Whitney U test. Bonferroni correction was performed for multiple comparisons. Receiver operating characteristic (ROC) curves were generated to assess the ability of hemodynamic variables to identify responders to fluid loading. The best ROC curve threshold was chosen as that which maximized the Youden index. Predictive accuracy was described based on AUROC using the standard terms: poor (0.6–0.7), fair (0.7–0.8), good (0.8–0.9), and excellent (0.9–1.0). The gray zone approach described by Coste *et al.* (25) was used to determine the range of the predictor within which a conclusive diagnosis regarding fluid responsiveness could not be made with sufficient certainty. Linear regression model was generated to test linear correlations among dynamic variables. Interobserver reproducibility for ΔVpeak was assessed using the intraclass correlation coefficient (ICC). The least significant change (LSC) was calculated from the coefficient of variation to characterize the minimum ΔVpeak change to detect a real change. The performance of predictors in predicting fluid responsiveness with an alternative ΔVpeak threshold other than 15% was also explored. A sensitivity analysis of the accuracy of the dynamic preload variables was conducted in patients aged between 4 and 6 years. $P<0.05$ was considered statistically significant.

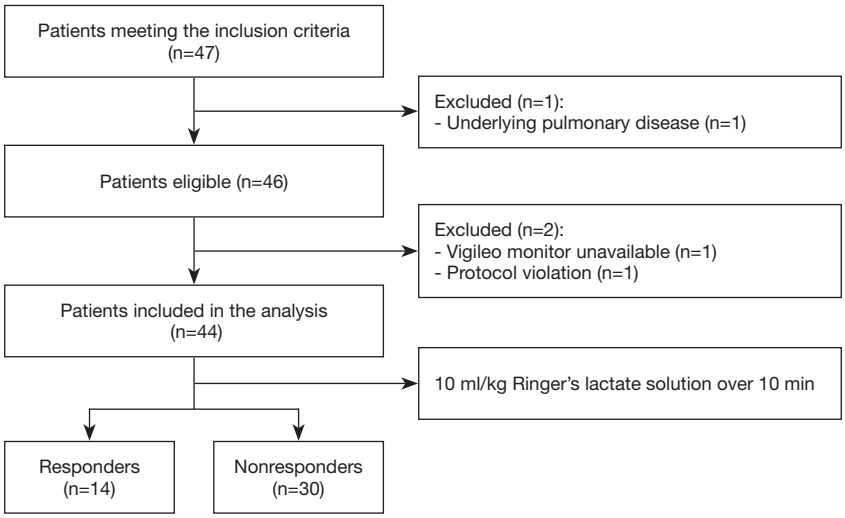

Figure 1 Study flowchart.

All statistical analyzes were performed using SPSS software (SPSS Version 26, Chicago, IL, USA) and MedCalc software (MedCalc Version 19.8, Ostend, Belgium).

Results

During the study period, 46 patients were eligible for the enrollment (*Figure 1*). Two patients were excluded because of unavailable Vigileo monitors or protocol violation. Therefore, 44 patients were included in the final analysis. The clinical characteristics of the cohort are shown in Table 1. No patients received vasoactive medication during the period of the experimental protocol.

Of the patients included, 14 (31.8%) showed a ΔVpeak >15% before fluid loading and were defined as responders. The cohort's median (IQR) ΔVpeak at baseline was 9.7% (6.5% to 15.8%). R had a higher baseline ΔVpeak than NR [18.2% (16.0% to 22.2%) *vs.* 7.9% (6.3% to 10.3%); P<0.001]. Demographic data and clinical characteristics revealed no differences between R and NR (*Table 1*).

Twenty (45.5%) showed an increase in MAP of >10% following fluid loading and were defined as responders. The median (IQR) increase in MAP was 9.3% (0.6–18.5%). R had a greater increase in MAP than NR [15.2% (10.2–18.5%) *vs.* 6.3% (–2.7–12.9%); P<0.001].

Hemodynamics during fluid loading

Before fluid loading, only the PVI value was significantly different between R and NR (P=0.017) (*Table 2*). Fluid loading significantly changed MAP, PVI, PPV, and SVV in both R and NR. However, SAP increased following fluid loading in R only. The R group showed a significantly greater absolute change in PPV and SVV after fluid loading from baseline compared with the NR group {absolute PPV change: 3 [1–4] and 4 [3–5] for NR and R, respectively, P=0.021; SVV: absolute SVV change: 2 [1–4] and 3 [3–5] for NR and R, respectively, P=0.040} (*Figure 2*). There was strong correlation between PVI and ΔVpeak at baseline (r=0.37, P=0.015) (*Figure 3*).

Prediction of fluid responsiveness defined by baseline ΔVpeak

The results of ROC curve analysis for hemodynamic variables to discriminate between R and NR with fluid responsiveness definition of a baseline ΔVpeak >15% are summarized in *Table 3* and *Figure 4A*. Baseline PVI showed fair diagnostic accuracy for fluid responsiveness defined by a baseline ΔVpeak >15%, with an AUROC value of 0.735 (95% CI: 0.560–0.857, P=0.002). A baseline PVI cutoff value of >13% (95% CI: 12–18%) predicted fluid responsiveness with a sensitivity of 93% and a specificity of 60%. The gray zone of PVI ranged between 12% and 20%, which included 43.8% of patients. Baseline PPV, SVV, PI, and Ea_{dyn} were not capable of predicting fluid responsiveness.

Sensitivity analysis

Ten (35.7%) of 28 patients in the 4–6 age subgroup showed

Table 1 Baseline patient characteristics among fluid responders and nonresponders (Medians or numbers)

Characteristic	Overall, n=44	R, n=14	NR, n=30	P
Age, mo	72 [60–96]	72 [60–108]	72 [60–96]	0.824
Female, n (%)	18 [40.9]	6 [46.2]	12 [38.7]	0.737
Height, cm	122 [112–130]	121 [110–130]	125 [112–128]	0.847
Weight, kg	25 [21–27]	25 [21–30]	24 [21–26]	0.469
BMI, kg/m^2	16.7 [15.4–17.7]	17.5 [16.1–18.7]	16.4 [15.4–17.7]	0.142
Ventilatory frequency, cycles/min	16 [15–18]	16 [15–18]	16 [15–18]	0.761
Peak inspiratory pressure, cmH_2O	14 [12–15]	14 [13–15]	14 [12–15]	0.774
Plateau pressure, cmH_2O	8 [7–9]	8 [8–9]	8 [7–9]	0.947
End-tidal CO_2 partial pressure	35 [32–36]	35 [32–36]	35 [33–36]	0.672
End-tidal sevoflurane concentration	0.8 [0.6–1.0]	1.0 [0.5–1.1]	0.8 [0.7–1.0]	0.875
Infusion rate of propofol, $mg·kg^{-1}·h^{-1}$	6.0 [5.0–7.0]	6.0 [5.0–7.0]	6.0 [5.0–7.0]	0.913
Infusion rate of remifentanil, $\mu g·kg^{-1}·min^{-1}$	0.13 [0.11–0.15]	0.13 [0.11–0.15]	0.14 [0.12–0.15]	0.221
Nasopharyngeal Temperature, ℃	36.2 [36.1–36.5]	36.2 [36.1–36.4]	36.2 [36.1–36.5]	0.937
HR/ventilatory frequency	4.4 [4.1–4.8]	4.3 [4.1–4.8]	4.4 [3.7–4.8]	0.867

*P<0.05, R *vs*. NR. R, responder; NR, nonresponder; BMI, body mass index; HR, heart rate.

Table 2 Hemodynamic measurements at baseline and after fluid loading among the responders and nonresponders (Medians)

Variable	R			NR			P R *vs.* NR, before	P R *vs.* NR, after
	Before fluid loading	After fluid loading	P before *vs.* after	Before fluid loading	After fluid loading	P before *vs.* after		
HR, beats/min	73 [70–74]	62 [56–76]	0.470	73 [62–86]	61 [53–83]	0.062	0.754	0.941
SAP, mmHg	100 [93–107]	107 [98–121]	0.003*	98 [91–120]	104 [99–120]	0.043	0.743	0.412
MAP, mmHg	69 [64–74]	76 [71–84]	0.002*	68 [65–81]	74 [66–86]	0.008*	0.732	0.549
PPV, %	10 [9–11]	7 [5–8]	<0.001*	9 [8–11]	7 [7–8]	<0.001*	0.451	0.262
SVV, %	9 [7–14]	6 [4–7]	<0.001*	8 [6–10]	6 [4–8]	<0.001*	0.483	0.651
PVI, %	16 [14–25]	13 [10–17]	0.008*	12 [12–18]	10 [8–16]	0.001*	0.017**	0.373
PI, %	3.7 [3.3–5.9]	5.0 [3.5–7.1]	0.090	3.8 [3.2–6.9]	5.4 [3.6–7.0]	0.057	0.797	0.599
Ea_{dyn}	1.1 [1.0–1.3]	1.2 [1.0–1.4]	0.197	1.2 [1.1–1.3]	1.3 [1.1–1.5]	0.136	0.391	0.588

*P<0.025, before *vs.* after fluid loading. **P<0.025, R *vs.* NR. Bonferroni correction for multiple comparisons (twice per variable) decreased the threshold for significance to 0.025. R, responder; NR, nonresponder; Ea_{dyn}, dynamic arterial elastance; HR, heart rate; SAP, systolic arterial pressure; MAP, mean arterial pressure; PPV, pulse pressure variation; SVV, stroke volume variation; PVI, plethysmographic variation index; PI, perfusion index.

fluid responsiveness defined by a baseline ΔVpeak >15%, compared with 4 (25.0%) of 16 patients in the 7–9 age subgroup (P=0.463). In the 4–6 subgroup analysis, the results were essentially comparable with those of the whole cohort (*Table 3* and *Figure 4B*). PVI was a good predictor of fluid responsiveness with an improved AUROC of 0.792 in the patients aged 4–6 years and no change was detected in terms of the optimal PVI threshold value. PPV, SVV, PI, and Ea_{dyn} were not predictors of fluid responsiveness in the 4–6 age group.

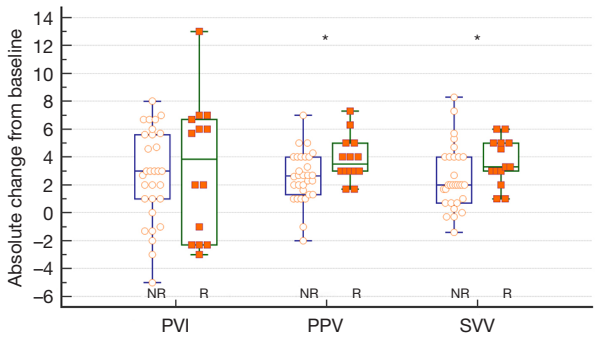

Figure 2 Box plots (for medians and interquartile ranges) showing absolute changes of the hemodynamic values from baseline in R and NR to fluid loading. *P<0.05, R *vs.* NR. R, responder; NR, nonresponder; PVI, plethysmographic variability index; PPV, pulse pressure variation; SVV, stroke volume variation. Open circles and filled squares represent individual values for each category.

The diagnostic accuracy and the cutoff threshold of PVI according to incremental ΔVpeak cutoff values to define a positive fluid response did not differ significantly (*Table 4*).

Prediction of fluid responsiveness defined by a MAP increase

Baseline ΔVpeak and SVV demonstrated fair predictive values for fluid responsiveness defined by an increase in MAP of >10% following fluid loading, with the optimal cutoff baseline ΔVpeak of 12.5% and SVV of 9 (AUROC =0.758 and 0.715, respectively) (*Table 5* and *Figure 5*). PPV, PVI, and Ea_{dyn} were poor predictors for a MAP increase of >10% following fluid loading.

Agreement analysis

Interobserver reproducibility for the measurements of baseline aortic blood flow peak velocity were acceptable (ICC 0.95, 95% CI: 0.94–0.96). The coefficient of variations for baseline ΔVpeak from two observers were 10.0% (95% CI: 7.5–12.5%) and 8.7% (95% CI: 6.3–11.1%), respectively. The mean LSC for baseline aortic blood flow peak velocity was 13.2%.

Discussion and conclusion

Our results demonstrated that, baseline PVI was a fair dynamic predictor of fluid responsiveness after induction defined by a baseline ΔVpeak of >15%, in children aged

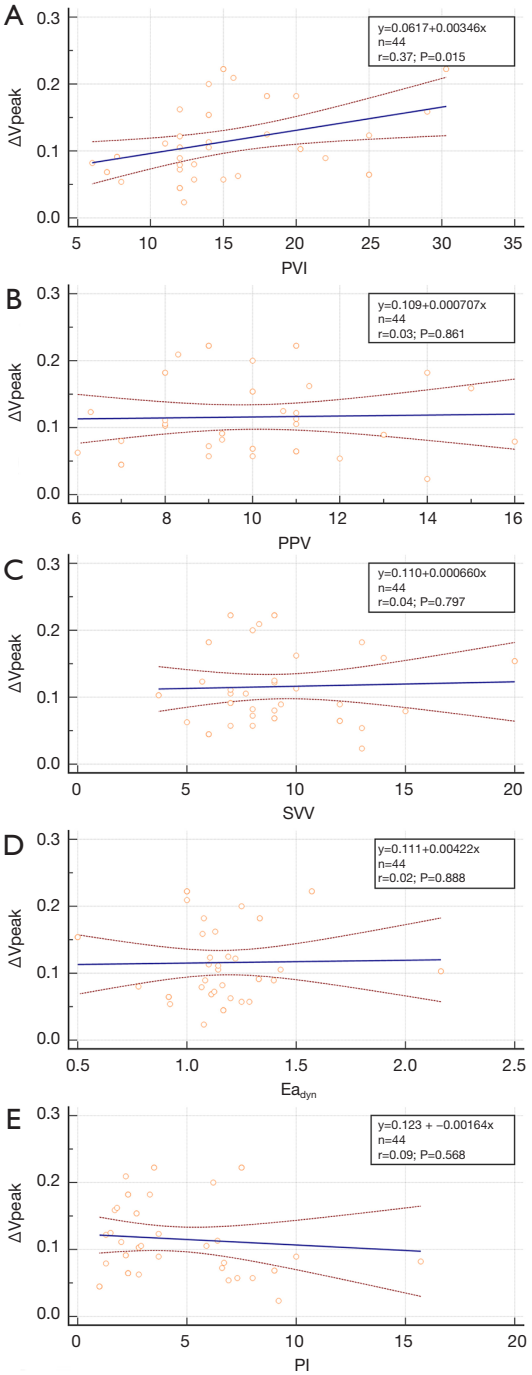

Figure 3 Correlation between hemodynamic variables and ΔVpeak at baseline. Dotted lines represent the estimate statistical formula derived from linear regression analysis. (A), PVI *vs.* ΔVpeak; (B), PPV *vs.* ΔVpeak; (C), SVV *vs.* ΔVpeak; (D), Ea_{dyn} *vs.* ΔVpeak; (E), PI *vs.* ΔVpeak. Ea_{dyn}, dynamic arterial elastance; PI, perfusion index; PVI, plethysmographic variability index; PPV, pulse pressure variation; SVV, stroke volume variation; ΔVpeak, respiratory variation in aortic blood flow peak velocity.

Table 3 Comparisons of the AUROCs, sensitivity, specificity, and optimal threshold values for PPV, SVV, and PVI to predict fluid responsiveness defined by ΔVpeak >15% in overall patients and 4–6 age subgroup

	AUROC (95% CI)	P	Sensitivity (%)	Specificity (%)	Optimal threshold
Overall (n=44, R=14, NR=30)					
PVI	0.735 (0.560–0.857)	0.002*	93	60	13%
PPV	0.560 (0.395–0.738)	0.509	100	20	7%
SVV	0.608 (0.425–0.785)	0.245	29	90	12%
Ea_{dyn}	0.581 (0.347–0.770)	0.447	57	77	1.1
PI	0.514 (0.345–0.678)	0.872	0	80	1.5%
4–6 age subgroup (n=28, R=10, NR=18)					
PVI	0.792 (0.580–0.925)	<0.001*	90	72	13%
PPV	0.533 (0.272–0.746)	0.785	100	22	7%
SVV	0.514 (0.275–0.708)	0.905	90	22	10%
Ea_{dyn}	0.561 (0.289–0.816)	0.650	40	100	1.3
PI	0.644 (0.426–0.831)	0.169	100	33	1.5%

*P<0.05, compared with an AUROC of 0.5. AUROC, area under the receiver operating characteristic curve; CI, confidence interval; R, responder; NR, nonresponder; Ea_{dyn}, dynamic arterial elastance; PPV, pulse pressure variation; SVV, stroke volume variation; PI, perfusion index; PVI, plethysmographic variation index; ΔVpeak, respiratory variation in aortic blood flow peak velocity.

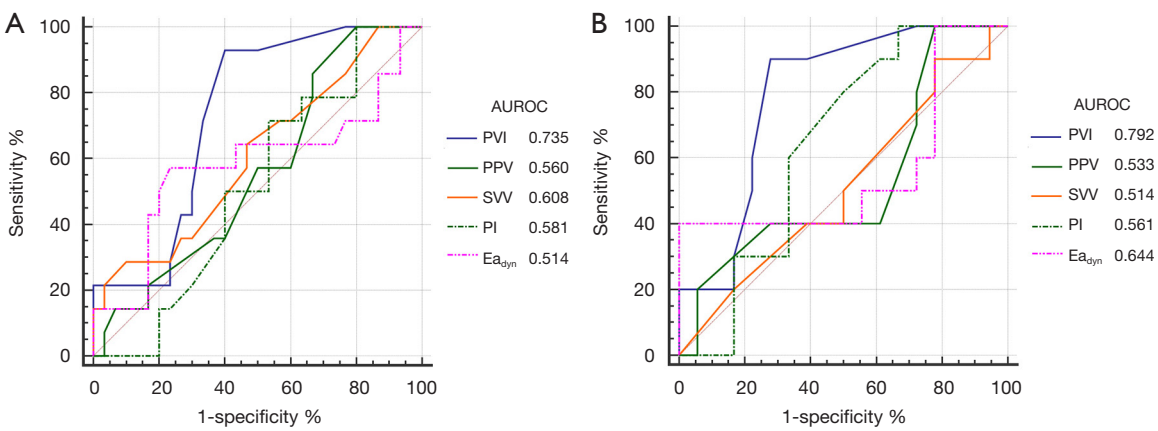

Figure 4 Comparison of the ROC curves for baseline hemodynamic variables (PVI, PPV, SVV, PI, and Ea_{dyn}) to discriminate fluid responders and nonresponders defined by a baseline ΔVpeak >15%. (A), overall patients; (B), the 4–6 age subgroup. Ea_{dyn}, dynamic arterial elastance; PI, perfusion index; PVI, plethysmographic variability index; PPV, pulse pressure variation; SVV, stroke volume variation; ΔVpeak, respiratory variation in aortic blood flow peak velocity; ROC, receiver operating characteristic curve; AUROC, area under the receiver operating characteristic curve.

4–9 years undergoing epileptogenic lesion excision. Baseline ΔVpeak and SVV had fair predictive values for a response of a MAP increase of >10% following fluid loading.

As a dynamic variable based on volume, not pressure, conflicting results have been obtained among investigations on the predictive values of PVI in the pediatric population. Two positive studies in children aged <10 years receiving neurosurgery or open surgery revealed that, PVI was accurate when used to predict fluid responsiveness (9,16). They were conducted in otherwise healthy patients similar

Table 4 The ROC curve analysis of baseline PVI according to incremental cutoff values for baseline ΔVpeak to define fluid responders

ΔVpeak thresholds (%)	R/NR	AUROC (95% CI)	P	Sensitivity (%)	Specificity (%)	Optimal threshold (%)
10	23/21	0.735 (0.547–0.860)	0.003*	83	71	13
11	19/25	0.707 (0.523–0.844)	0.009*	84	64	13
12	17/27	0.749 (0.566–0.873)	<0.001*	88	63	13
13–15	14/30	0.735 (0.560–0.857)	0.002*	93	60	13
16	11/33	0.720 (0.558–0.862)	0.006*	82	67	14
17–18	10/34	0.766 (0.598–0.886)	<0.001*	90	68	14
19	7/37	0.732 (0.569–0.880)	0.010*	100	51	13
20	6/38	0.765 (0.570–0.921)	0.003*	100	63	14

*P<0.05, compared with an AUROC of 0.5. R, responder; NR, nonresponder; ROC, receiver operating characteristic; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; PVI, plethysmographic variability index; ΔVpeak, respiratory variation in aortic blood flow peak velocity.

Table 5 Comparisons of the AUROCs, sensitivity, specificity, and optimal threshold values for ΔVpeak, PPV, SVV, PI, PVI, and Eadyn to predict fluid responsiveness defined by an increase in mean arterial pressure of >10% following fluid loading

	AUROC (95% CI)	P	Sensitivity (%)	Specificity (%)	Optimal threshold
ΔVpeak	0.758 (0.588–0.891)	<0.001*	60	92	12.5%
PVI	0.667 (0.475–0.814)	0.045*	80	63	13%
PPV	0.686 (0.511–0.839)	0.023*	55	79	11%
SVV	0.715 (0.533–0.849)	0.006*	50	88	9%
PI	0.518 (0.324–0.689)	0.844	85	38	2.2%
Ea_{dyn}	0.686 (0.501–0.859)	0.044*	55	96	1.1

*P<0.05, compared with an AUROC of 0.5. AUROC, area under the receiver operating characteristic curve; CI, confidence interval; R, responder; NR, nonresponder; Ea_{dyn}, dynamic arterial elastance; PPV, pulse pressure variation; SVV, stroke volume variation; PI, perfusion index; PVI, plethysmographic variation index; ΔVpeak, respiratory variation in aortic blood flow peak velocity.

to our cohort, and the results also concurred with ours. In contrast, a previous study investigated PVI's ability to predict a positive response to a bolus of 20 mL/kg normal saline after induction in neurosurgical patients aged 0–6 and 6–14 years, and failed to demonstrate its predictive value (15). The discrepancies observed between the above study and our study can be explained by the heterogeneity of the studied population and different interventions. In addition, their study may be underpowered by insufficient subject numbers in each age strata. Volume-based PVI is expected to be more sensitive to ventilator-induced changes than pressure-derived PPV or SVV in children. In addition to periodic change in SV during mechanical ventilation, the increased resistance to venous return during inspiration may increase the volume of venous blood, thus exaggerating the decrease in plethysmographic wave amplitude (26). However, it should be noted that PVI is affected by many factors related to PI, such as vasoactive drugs, hypothermia, anxiety, cardiac arrhythmia, and sampling site, contacting force. A PI >4% improves the validity of PVI values (27). Fifty-three percent of our cohort showed PI values <4%, and the predictive reliability of PVI in the present study must be interpreted with caution. In addition, its gray zone includes a considerable number of patients.

Hemodynamic monitoring techniques measuring cardiac out and SVV currently assessed in pediatric population include esophageal Doppler technique (USCOM), transesophageal echocardiography, thoracic electrical bioimpedance devices, pulse contour analysis (PiCCO and Mostcare), and bioreactance devices (NICOM),

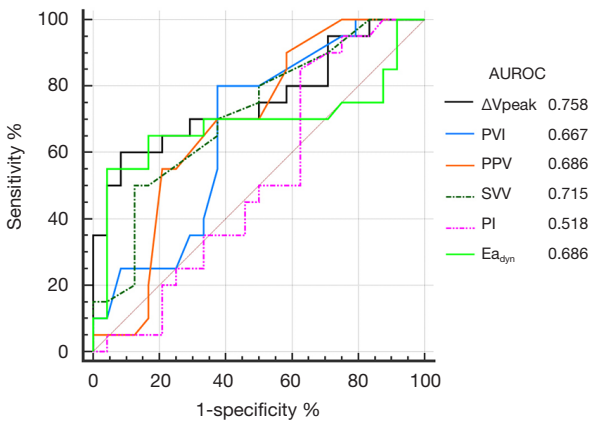

Figure 5 Comparison of the ROC curves for baseline hemodynamic variables (ΔVpeak, PVI, PPV, SVV, PI, and Ea_{dyn}) to discriminate fluid responders and nonresponders defined by an increase in mean arterial pressure of >10% following fluid loading. Ea_{dyn}, dynamic arterial elastance; PI, perfusion index; PVI, plethysmographic variability index; PPV, pulse pressure variation; SVV, stroke volume variation; ΔVpeak, respiratory variation in aortic blood flow peak velocity; ROC, receiver operating characteristic curve; AUROC, area under the receiver operating characteristic curve.

with varying diagnostic values of SVV in predicting fluid responsiveness. Because of the diverse SVV algorithms in proprietary monitors, interventions, and patient characteristics, the pediatric studies investigating the predictive value of the SVV for fluid responsiveness are almost incomparable to each other (14,22,28-31). A meta-analysis of SVV application in children examined studies using PiCCO, USCOM, NICOM, and Mostcare, and concluded that, SVV was of diagnostic value in predicting fluid responsiveness in children under mechanical ventilation (32). However, authors considered that further studies are needed to confirm the predictive values of SVV because of high heterogeneity of studies and mainly cardiosurgical and intensive care pediatric patients included. One positive study measuring SVV using NICOM enrolled patients similar to the present study by including patients aged 0–16 years undergoing craniosynostosis repair (29). The discrepancies observed between the above study and ours can be explained by age difference in the studied populations, type and volume of fluid infused, and proprietary monitors. We applied a tidal volume of 8 mL/kg with a PEEP of 4 cmH_2O as clinical routines to induce a minimum meaningful intrathoracic pressure swing. It might be possible that higher values of a tidal volume and no PEEP applied would improve the predictive performance of SVV regarding fluid responsiveness. Increased arterial compliance in children, compared with adults, partially absorbs the magnitude of change in arterial blood pressure caused by an increase in SV during positive pressure ventilation. That may partly explain PPV and SVV's failure to predict fluid responsiveness defined by a baseline ΔVpeak of >15%.

Although baseline PPV was not found to be useful for predicting fluid responsiveness after anesthesia induction in our study, responders had great absolute changes in the PPV and SVV values from baseline compared with nonresponders. The mini-fluid challenge is a clinical method of predicting fluid responsiveness by rapidly infusing small amount of intravenous fluids, and assessing its systemically hemodynamic effect. This method is meant to predict if a patient will respond to a subsequent, larger fluid challenge with a significant increase in SV. Further investigation is required to evaluate, whether a mini-fluid challenge test determining the change in PPV before and after fluid challenge would be helpful, in discriminating fluid responsiveness in children with a PVI value in gray zone and guiding optimal perioperative fluid management in children (33).

The present study demonstrated that the patients aged 4–6 years had an improved AUROC of PVI for predicting fluid responsiveness compared to that in the overall patients, although this result might be underpowered by limited patient numbers. The pediatric population includes different age groups that may vary in dynamic variables' predictive reliabilities and optimal cutoffs regarding fluid responsiveness. This is partly because of the children's varying physiologic characteristics with increasing age, related to cardiopulmonary development and vascular compliance change (34-36). More subjects are required to establish age-specific predictors and optimal cutoff values.

The adequate intraoperative MAP is crucial for modern anesthetic care (37). Arterial pressure is dependent on the interaction between left ventricular SV and arterial tone. Given comparative arterial tones (reflected by Ea_{dyn}) between R and NR, arterial pressure might be significantly associated with stroke volume in the present study. That may explain why baseline ΔVpeak was found to be a fair predictor of a MAP increase following fluid loading in our cohort. We also found that baseline SVV, not PVI, fairly predicted a MAP increase following fluid challenge. Different from volume-based PVI, SVV calculated using

FloTrac/Vigileo is pressure-derived, which reflects the variation of standard deviation in pulse pressure. Further studies are needed to explore the relationship between ΔVpeak or SVV and MAP in pediatric population.

The most common reference standard for the definition of fluid responsiveness is a change in SV of greater than 15% as measured by transesophageal or transthoracic echocardiography. ΔVpeak is the only variable to consistently predict fluid responsiveness in children with an AUROC of 0.8–1.0 (1,9-12). We decided to use baseline ΔVpeak to distinguish responders from nonresponders, instead of SV measurement. One single echocardiographic measurement of ΔVpeak has the potential to reduce intra- and interobserver variability and echocardiographic measurement errors related to two operator-dependent measurements required for SV determination. No unequivocal cutoff values for baseline ΔVpeak to define fluid responsiveness have been determined in the literature to date. The reported threshold values vary considerably across the studies from 7% to 20% (1,9-12). Two previous studies demonstrated that ΔVpeak threshold values of 10% and 11% respectively reliably predicted an increase in SV of >15% to fluid loading in a comparable patient population (9,15). In the present study, we arbitrarily defined responders with baseline ΔVpeak >15%, which is a high limit of the cutoff values previously reported, aiming to avoid falsely positive fluid responsiveness detection. In addition, 15% is more than the expected error of echocardiographic ΔVpeak measurements and is generally considered clinically relevant. A baseline ΔVpeak threshold value of 15% was reasonably justified by the LSC of 13.2%.

Limitations

First, the current study had a small cohort and was conducted in a single tertiary hospital. Second, although decreased intravascular volume after anesthesia induction is common, the majority of elective patients are no more than moderately dehydrated with no or mild clinical signs of volume depletion. Pediatric patients with significant clinical signs of hypovolemia might yield different results. Last, the FloTrac/Vigileo cardiac output monitoring system is not validated for cardiac index monitoring in the pediatric setting. However, according to the SV formula ($SV = PP_{SD} \times K$), the imprecise SV measurements come from an inaccurate K. Any error in this method would only affect the precision of the maximum and minimum values of SV, but not the ratio of (SVmax–SVmin)/SVmean. SVV is therefore not subject to algorithm errors.

In conclusion, baseline PVI showed fair reliability to predict fluid responsiveness, defined by a baseline ΔVpeak of >15%, after anesthesia induction in mechanically ventilated children aged 4–9 years undergoing major neurosurgery. Baseline PPV, FloTrac/Vigileo-derived SVV, and Ea_{dyn} did not accurately predict fluid responsiveness reflected by a baseline ΔVpeak of >15%. Baseline ΔVpeak and SVV were fair predictors for an increase in MAP following fluid loading.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://dx.doi.org/10.21037/tp-21-281

Data Sharing Statement: available at https://dx.doi.org/10.21037/tp-21-281

Peer Review File: Available at https://dx.doi.org/10.21037/tp-21-281

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tp-21-281). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of Peking University First Hospital, Beijing, China (Chairperson Prof YY Yu; ethical number: 2020-061). The study was registered prior to patient enrollment with the Chinese Clinical Trial Registry on May 25, 2020 (ChiCTR identifier: ChiCTR2000033245; principal investigator: Lin-Lin Song). And informed consent was taken from all patients' parent or legal guardian.

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Cite this article as: Song LL, Geng ZY, Ma W, Liu YF, Wang DX. Dynamic variables predict fluid responsiveness in pre-school and school children undergoing neurosurgery: a prospective observational study. Transl Pediatr 2021;10(11):2972-2984. doi: 10.21037/tp-21-281