

Prediction of fluid responsiveness in mechanically ventilated children undergoing neurosurgery

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Editor's key points

- Pulse pressure variation and other dynamic measures of fluid responsiveness are increasingly popular in adults, but there are few data in children.
- In this study, changes in pleth variability index and aortic blood flow velocity predicted fluid responsiveness to a 10 ml kg⁻¹ infusion of colloid during surgery.
- These associations were modest; other variables including systolic and pulse pressure variations were not predictive.

Background. The purpose of this study was to evaluate the clinical usefulness of static and dynamic variables for the prediction of fluid responsiveness in children under general anaesthesia.

Methods. Thirty-three mechanically ventilated children received 10 ml kg⁻¹ colloid for 10 min while stable during surgery. Arterial pressure, heart rate, central venous pressure (CVP), and pleth variability index (PVI), in addition to variation in systolic pressure, pulse pressure (including Δ down and Δ up), respiratory aortic blood flow velocity (Δ Vpeak), and inferior vena cava diameter were measured before and after volume expansion. Patients were classified as responders to fluid loading if their stroke volume index (SVI) increased by at least 10%.

Results. There were 15 volume responders and 18 non-responders. Of the variables examined, Δ Vpeak ($r=0.516$, $P=0.004$) and PVI ($r=0.49$, $P=0.004$) before volume expansion were significantly correlated with changes in SVI. The receiver-operating characteristic (ROC) curve analysis showed that PVI and Δ Vpeak predicted fluid responsiveness. Areas under the ROC curves of PVI and Δ Vpeak were statistically larger than that of CVP ($P=0.006$ and 0.014 , respectively). However, those of other variables were similar to that of CVP.

Conclusions. Δ Vpeak and PVI can be used to predict fluid responsiveness in mechanically ventilated children under general anaesthesia. The other static and dynamic variables assessed in this study were not found to predict fluid responsiveness significantly in children.

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The correct assessment of intravascular volume and adequate maintenance of cardiac preload can improve the outcomes of critically ill patients. Conversely, inappropriate fluid loading can be harmful, and therefore, many studies have sought to identify predictors of fluid responsiveness. Static variables, such as central venous pressure (CVP), pulmonary capillary wedge pressure, and left ventricle end-diastolic area, do not predict fluid responsiveness.^{1–6} However, dynamic indicators of fluid responsiveness that are based on cardiopulmonary interactions in patients ventilated mechanically, such as respiratory variations in aortic blood flow peak velocity (Δ Vpeak), respiratory variations in inferior vena cava diameter (Δ IVCD), systolic pressure variation (SPV), pulse pressure variation (PPV), difference between SPref and SPmin (Δ down), difference between SPmax and SPref (Δ up),

and pleth variability index (PVI), have been shown to be predictive.^{1 2 5–11}

There are insufficient data on the efficacy of these dynamic variables for the prediction of fluid responsiveness in children.^{10 12–14} Children differ from adults in terms of arterial compliance, chest wall rigidity, and lung compliance, and therefore, indicators based on pressure, such as PPV and SPV may not be as reliable in children.

PVI is an automatic and continuous index of respiratory variations in pulse oximeter plethysmographic waveform amplitude. PVI has been shown to predict fluid responsiveness in mechanically ventilated adult patients and has potential clinical applications.^{7 8 15–18} PVI can be used to non-invasively determine patient volume status and is based on volume not pressure. Therefore, the use of PVI to

predict fluid responsiveness in paediatric patients is theoretically sound, but more data are required to support this assertion.

The purpose of this study was to evaluate the predictive values of CVP, SPV, PPV, Δ up, Δ down, Δ Vpeak, Δ IVCD, and PVI for the determination of fluid responsiveness in paediatric patients during general anaesthesia.

Methods

This study was approved by the appropriate institutional review boards, and written informed consent was obtained from parents or parents and patients when patients were old enough to understand the study. Children aged 6 months to 9 yr of age undergoing elective neurosurgery under general anaesthesia were enrolled in this study. Patients were excluded if they had congenital heart disease, cardiac arrhythmia, ventricular dysfunction, unstable perfusion index (PI) (defined as a variation exceeding 30% over a 1 min period), pneumonia, atelectasis, upper respiratory infection symptoms, or vasoactive and/or inotropic support.

Anaesthesia was induced with thiopental (5–6 mg kg⁻¹), remifentanyl (0.3–1.0 µg kg⁻¹), and inhaled sevoflurane. Rocuronium (0.6 mg kg⁻¹) was administered to facilitate tracheal intubation. Mechanical ventilation was instituted in a pressure-controlled mode adjusted to obtain a P_{aCO_2} of 4.7–5.3 kPa during surgery. PEEP was not applied. Anaesthesia was maintained with 1–2 vol% sevoflurane and by a continuous infusion of remifentanyl (0.1–0.2 µg kg⁻¹ min⁻¹). After induction of anaesthesia, a central venous catheter was placed in the right subclavian vein. Ultrasound was used to confirm that the catheter tip had been positioned in the superior vena cava and not in the internal jugular vein, and if the catheter tip had been placed in the internal jugular vein, it was repositioned in the superior vena cava under ultrasound guidance.¹⁹ An arterial catheter was placed in the radial artery, and pressure transducers were positioned on the mid-axillary line. Oxygen saturation was measured continuously using the Masimo Rainbow SET[®] monitoring system (Radical 7, software version V7.6.2.2, Masimo Corp., Irvine, CA, USA). A pulse oximeter probe (used to measure PVI) was placed on the index finger of the hand without an arterial cannula and was covered with an impermeable black shield to prevent optical interference. A circulating-water blanket and a forced-air warming system (Bair Hugger Warming system, Augustine Medical, Eden Prairie, MN, USA) were applied in order to avoid hypothermia. In particular, the hand with the pulse oximeter probe was kept warm. Body temperature was measured using an oesophageal stethoscope.

Peak inspiratory pressure (PIP) was recorded. In addition, the waveforms of routine haemodynamic variables [heart rate (HR), arterial pressure, CVP] and end-tidal carbon dioxide ($P_{E'CO_2}$) were recorded using a bedside monitor (Solar 8000M, GE Medical Systems Information Technologies, Milwaukee, WI, USA) connected to a computer using data collection software (CIC, GE Medical Systems Information

Technologies). End-tidal sevoflurane concentration was also measured.

Pressure measurements

Maximal pulse pressure (PPmax), minimal pulse pressure (PPmin), maximal systolic pressure (SPmax), minimal systolic pressure (SPmin), and reference systolic pressure at the end expiratory pause (SPref) at the end-expiratory pause were manually measured. Each parameter was measured three times during three consecutive respiratory cycles by a single blinded investigator and averages were used for statistical analysis. SPV (%) = $100 \times (SP_{max} - SP_{min}) / [(SP_{max} + SP_{min}) / 2]$, PPV (%) = $100 \times (PP_{max} - PP_{min}) / [(PP_{max} + PP_{min}) / 2]$, Δ down = SPref – SPmin, and Δ up = SPmax – SPref.

Pleth variability index

Red and infrared light are used by a pulse oximeter to measure oxygen saturation. A constant amount of light (DC) from the pulse oximeter is absorbed by skin, other tissues, and non-pulsatile blood, whereas a variable amount (AC) is absorbed by pulsatile arterial inflow. The PI is calculated from the absorptions of red and infrared light, using: PI (%) = $(AC/DC) \times 100$. AC and DC signals are extracted from the amplitude of the plethysmographic waveform. The dynamic change in PI during a respiratory cycle results in the PVI, which was automatically calculated using: $PVI = 100 \times (PI_{max} - PI_{min}) / PI_{max}$. PVI reflects respiratory variations in PI.

Echocardiographic measurements: stroke volume index, Δ Vpeak, and Δ IVCD

Echocardiographic variables were derived from transthoracic echocardiography (Vivid 7 Pro, GE Vingmed Ultrasound AS, Horten, Norway), and all measurements were made by a single investigator.

Stroke volume index

Aortic annulus diameter (D) was measured during systole in the parasternal long-axis view. Aortic valve area was calculated using $\pi (D/2)^2$. Pulsed Doppler waves of aortic blood flow were recorded at the level of the aortic annulus with the ultrasound parallel to aortic blood flow in the apical five-chamber view. Aortic velocity–time integral (VTI) was calculated from the mean of three consecutive waves measured at the end of the expiratory period. The mean of three VTI values measured from three consecutive respiratory cycles was used for statistical analysis. Stroke volume index (SVI) was calculated as: $SVI = \text{aortic valve area} \times \text{the VTI of aortic blood flow/body surface area}$.^{10 12 13 18}

Δ Vpeak

Δ Vpeak was determined from pulsed Doppler waves of aortic blood flow during the respiratory cycle. The maximum and minimum peak aortic blood flow velocities (Vpeak max and Vpeak min) were measured. Δ Vpeak was calculated as

$\Delta V_{\text{peak}} (\%) = 100 \times (V_{\text{peak max}} - V_{\text{peak min}}) / [(V_{\text{peak max}} + V_{\text{peak min}}) / 2]$. The mean ΔV_{peak} was measured for three consecutive breaths and used in the analysis.

Δ Inferior vena cava diameter

The IVCD was measured from the subcostal view (~2 cm from the right atrium) using M-mode. The maximum and minimum IVCD (IVCDmax and IVCDmin) over a single respiratory cycle were recorded. Δ IVCD was calculated as $\Delta \text{IVCD} (\%) = 100 \times (\text{IVCDmax} - \text{IVCDmin}) / [(\text{IVCDmax} + \text{IVCDmin}) / 2]$, and was measured three times during three consecutive respiratory cycles. The mean values were used in the analysis.

Experimental protocol

After confirming no active bleeding and a 5 min period of haemodynamic stability (arterial pressure and HR stabilized to $\pm 5\%$) in the middle of surgery, PIP was adjusted to obtain an expiratory tidal volume of 10 ml kg^{-1} , as used in previous studies.^{10–13} All variables were then measured before fluid loading. Volume expansion was conducted by administering 10 ml kg^{-1} of colloid solution (Volumen, hydroxyethyl starch, Fresenius Kabi, India) for 10 min, and then all variables were remeasured. If necessary, the ventilatory protocol was changed to achieve a P_{aCO_2} of 4.7–5.3 kPa after data acquisition. No changes in anaesthetic dose were made during measurements.

Statistical analysis

The required sample size was calculated using PASS software based on data from a previous paediatric study.¹⁰ In this previous study, the ratio between responders and non-responders was 11:10 and the area under the receiver-operating characteristic (ROC) curve for ΔV_{peak} was 0.83. Accordingly, the sample size required for the present study was 26 to detect a difference of 0.3 in the area under the ROC using the two-tailed *t*-test with an α -error of 0.05 and a power of 0.8.^{20–21} All statistical analyses were performed using SPSS software (SPSS, Chicago, IL, USA) and MedCalc software (MedCalc 10.0, Mariakerke, Belgium). Subjects with at least a 10% increase in SVI after volume expansion were defined as responders.^{22–26} Normalities of data distributions were confirmed using the Kolmogorov–Smirnov test. Variables were compared before and after volume expansion using the paired *t*-test. The differences between responders and non-responders were evaluated using the Student's *t*-test or the Mann–Whitney *U*-test. Multiple testing corrections were performed using the 'False Discovery Rate' method.²⁷ Spearman's rank method was used to test linear correlations. ROC curves were generated for all variables and area under the ROC curve was calculated and compared using the Hanley–McNeil test.²¹ The predictive abilities of variables for fluid responsiveness were determined using the ROC curve analysis. Area under the ROC curve of each

parameter was compared with that of CVP. Statistical significance was accepted for *P*-values of <0.05 .

Results

Initially, we recruited 37 paediatric patients aged <9 yr undergoing neurosurgery and who required invasive arterial pressure and CVP monitoring. However, four of the 37 were excluded due to inadequate data acquisition, and thus, the study cohort comprised 33 patients (20 males and 13 females). Neurosurgery consisted of 19 encephaloduroarteriosynangioses for moyamoya disease, 12 brain tumour excisions, and two cranioplasties.

No patient received a vasoactive drug during surgery, including times of data acquisition. There were 15 volume responders and 18 non-responders. The clinical characteristics of responders and non-responders were similar, and no difference was observed between these two groups in terms of PIP, $P_{\text{E}'\text{CO}_2}$, end-tidal sevoflurane concentration, or temperature during measurements (Table 1). There were no significant differences in haemodynamic variables between responders and non-responders before fluid loading (Table 2). Fluid loading changed CVP, SPV, PPV, and Δ up in both responders and non-responders. However, ΔV_{peak} , PVI, and SVI were changed by volume expansion in the responders only. Only ΔV_{peak} ($r=0.516$, $P=0.004$) and PVI ($r=0.49$, $P=0.004$) before volume expansion were significantly correlated with SVI change. However, other variables before fluid loading were not correlated with SVI change.

The results of ROC curve analysis are summarized in Table 3. ΔV_{peak} and PVI were found to be the best and second best variables, respectively, for predicting a 10% increase in SVI. In particular, a ΔV_{peak} of $>11\%$ was able to predict fluid responsiveness with a sensitivity of 86.7% and a specificity of 72.2%, and a PVI value of $>11\%$ predicted fluid responsiveness with a sensitivity of 73.3% and a specificity of 86.7%.

When areas under the ROC of all parameters were compared with that of CVP, those of ΔV_{peak} and PVI were significantly different from that of CVP ($P=0.006$ and 0.014 , respectively). However, those of other variables were similar to that of CVP (Fig. 1).

Table 1 Patient characteristics and intraoperative variables expressed as mean (SD) unless specified. PIP, peak inspiratory pressure; $P_{\text{E}'\text{sevo}}$, end-tidal sevoflurane concentration

	Responders (n=15)	Non-responders (n=18)
Age [mean (range) months]	74.1 (7–120)	70.4 (9–120)
Weight (kg)	24.3 (10.2)	23.0 (9.2)
Height (cm)	115.7 (22.8)	116.1 (120.4)
PIP (cm H ₂ O)	18.2 (2.7)	18.9 (2.2)
$P_{\text{E}'\text{CO}_2}$ (kPa)	5.1 (0.2)	5.1 (0.2)
$P_{\text{E}'\text{sevo}}$ (vol%)	1.69 (0.14)	1.68 (0.15)
Temperature (°C)	36.8 (0.2)	36.5 (0.2)

Table 2 Haemodynamic and dynamic variables expressed as mean (sd). VE, volume expansion; SAP, systolic arterial pressure; HR, heart rate; CVP, central venous pressure; Δ IVCD, respiratory variation of inferior vena cava diameter; SPV, systolic pressure variation; PPV, pulse pressure variation; Δ Vpeak, respiratory variation of aortic blood flow velocity; PVI, pleth variability index; SVI, stroke volume index; PI, perfusion index. * $P < 0.05$ before VE vs after VE. P -value was adjusted for multiple comparisons

	Responders (n=15)		Non-responders (n=18)	
	Before VE	After VE	Before VE	After VE
SAP (mm Hg)	97 (16)	99 (18)	88 (20)	92 (19)
HR (beats min ⁻¹)	105 (22)	100 (18)	101 (25)	99 (25)
CVP (mm Hg)	4.0 (1.9)	7.8 (2.1)*	4.5 (2.8)	7.8 (2.5)*
Δ IVCD (%)	12.5 (12.1)	13.4 (11.7)	14.4 (6.2)	11.5 (8.3)
SPV (%)	7.0 (3.7)	3.9 (1.9)*	6.1 (2.7)	4.1 (1.9)*
PPV (%)	9.8 (5.0)	5.6 (3.2)*	9.5 (5.3)	6.5 (3.9)*
Δ Down (mm Hg)	2.0 (1.1)	1.3 (0.6)	1.5 (1.0)	1.2 (1.1)
Δ Up (mm Hg)	4.8 (2.0)	2.6 (1.9)*	3.7 (1.8)	2.6 (1.0)*
Δ Vpeak (%)	14.1 (4.2)	9.8 (4.0)*	9.6 (4.9)	9.1 (4.4)
PVI (%)	17.2 (10.2)	12.1 (8.7)*	9.4 (5.7)	8.1 (6.9)
SVI (ml m ⁻²)	38.8 (10.8)	46.7 (13.1)*	41.9 (8.6)	42.7 (9.5)
PI	5.1 (3.2)	4.0 (2.5)	4.4 (2.7)	4.7 (3.2)

Table 3 The area under ROC curve for all variables. ROC, receiver operating characteristic; CI, confidence interval; SAP, systolic arterial pressure; HR, heart rate; CVP, central venous pressure; Δ IVCD, respiratory variation of inferior vena cava diameter; SPV, systolic pressure variation; PPV, pulse pressure variation; Δ Vpeak, respiratory variation of aortic blood flow velocity; PVI, pleth variability index; SVI, stroke volume index. * $P < 0.05$, area under ROC curve > 0.5 . † $P < 0.05$ vs area under the curve of CVP

	Area under the curve	95 %CI
SAP (mm Hg)	0.665	0.474–0.856
HR (beats min ⁻¹)	0.552	0.351–0.752
CVP (mm Hg)	0.469	0.230–0.707
Δ IVCD (%)	0.369	0.156–0.582
SPV (%)	0.578	0.378–0.777
PPV (%)	0.544	0.344–0.745
Δ Down (%)	0.624	0.422–0.825
Δ Up (%)	0.639	0.445–0.834
Δ Vpeak(%)	0.804*†	0.643–0.965
PVI (%)	0.767*†	0.597–0.936

Discussion

This study was undertaken to identify predictors of fluid responsiveness during surgery in children. Our results show that Δ Vpeak at a cut-off value of 11% and PVI at a cut-off of 11% can be used to predict fluid responsiveness during surgery in children. In contrast, the other indicators, such as CVP, Δ IVCD, SPV, PPV, Δ down, and Δ up, did not predict fluid responsiveness.

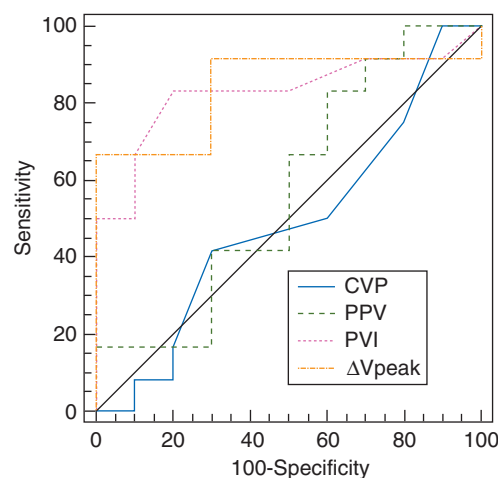


Fig 1 Comparison of areas under ROC curves before volume expansion. Areas under the ROC curve of Δ Vpeak and PVI are significantly larger than that of CVP before fluid loading ($P=0.006$ and 0.014 , respectively). However, that of PPV is similar to that of CVP before fluid loading. Areas under ROC curves were compared using the Hanley–McNeil test. CVP, central venous pressure; PPV, pulse pressure variation; PVI, pleth variability index; Δ Vpeak, respiratory variation of aortic blood flow velocity.

Dynamic variables are considered better predictors of fluid responsiveness than static variables. Of the dynamic variables, PPV has been consistently shown to be the best predictor of fluid responsiveness in adults. However, in this study, PPV was not found to be useful for predicting fluid responsiveness during general anaesthesia in children, which concurs with the findings of previous paediatric studies.^{12–14}

There are several possible explanations for the difference in the predictive value of PPV between children and adults. Arterial pulse pressure is dependent on stroke volume and arterial elastance, and the arterial pressure of a stiffer vessel more accurately reflects stroke volume. Arterial elastance in children is low, and therefore, pressures transmitted by an increase in stroke volume may be partially absorbed, and pressure variations caused by an increase in stroke volume may be absent from the arterial pressure waveform.

No previous study has assessed the utilities of SPV, Δ up, and Δ down for predicting volume responsiveness in ventilated children during surgery. However, according to our data, these variables are not useful predictors of fluid responsiveness in paediatric patients.

Δ Vpeak has previously been shown to be a good indicator of fluid responsiveness in many different clinical situations with cut-off values from 10% to 20%.^{2 10 12 13} These findings are consistent with the 11% cut-off identified in the present study, which had acceptable sensitivity and specificity. Δ Vpeak is likely to have some practical role for the prediction of fluid responsiveness in children because of its non-invasiveness and good predictability. However, the

most important limitation of ΔV_{peak} is that its value is dependent on the measurement skill of the echographer and the evaluator of recorded signals. In addition, clinicians should consider that ΔV_{peak} could be affected by cardiac rhythm, tidal volume, and the HR/ventilator frequency ratio.

Many studies have provided favourable and promising data on PVI for fluid responsiveness in adults in various clinical settings.^{8 15 16 18 22} However, the ability of PVI to predict fluid responsiveness seems limited in paediatric patients. In one study, PVI did not reach statistical significance for the prediction of fluid responsiveness in children in the operating theatre,¹³ whereas in another, PVI was found to predict fluid responsiveness in infants under mechanical ventilation.²⁸ Furthermore, in previous study on infants, it was shown that PVI at a cut-off of $>13\%$ can determine fluid responsiveness with a sensitivity of 84% and a specificity of 64%, which are similar to our results. In the present study, PVI with a cut-off of $>11\%$ was found to aid the differentiation of responders and non-responders with acceptable sensitivity and specificity.

In the present study, PVI was found to predict fluid responsiveness, but this has some limitations. PVI is affected by many factors related to PI, and the accuracy with which PVI predicts fluid responsiveness is reduced at lower PI values.²⁹ Furthermore, peripheral vasoconstriction caused by vasoactive drugs or hypothermia can decrease the reliability of PVI,³⁰ and cardiac arrhythmia limits the use of PVI, and of other dynamic predictors of fluid responsiveness. However, in the present study, PI values, temperature, and the use of vasoactive drug were similar for responders and non-responders, and therefore, bias associated with PI values can probably be excluded.

We used Doppler echocardiography to determine SVI. Echocardiographic methods have been frequently used in previous studies to measure cardiac output (CO) changes.^{10 12 13} Theoretically, measurements at the left ventricular outflow tract (LVOT) can more accurately determine SVI because it is rounder than aortic valve area. Therefore, it should be remembered that the formula $(D/2)^2\pi$ may not be applicable in the aortic valve area. However, in the present study, the important feature was SVI change induced by fluid administration rather than absolute SVI values. The Doppler sampling site should be easily determined and constant when measurements are taken before and after volume loading, and the aortic valve annulus is a more constant landmark for Doppler sampling than the LVOT. Accordingly, we used the aortic valve annulus rather than the LVOT.

One important limitation of this study is that SVI changes were determined in the same manner as ΔV_{peak} , namely by Doppler echocardiography. Thus, both measurements share the same methodological properties and may be more closely related, which could cause uncontrolled bias. However, CO is difficult to measure in the paediatric population, and thus, many other authors have used echocardiography to determine CO. Further study is required to compare different means of measuring CO and ΔV_{peak} .

In conclusion, ΔV_{peak} and PVI are predictive of fluid responsiveness in mechanically ventilated children under general anaesthesia. However, the other dynamic variables examined are not significant predictors of fluid responsiveness in children.

Declaration of interest

None declared.

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