

PAEDIATRICS

# Predicting fluid responsiveness in mechanically ventilated children under general anaesthesia using dynamic parameters and transthoracic echocardiography

E. Pereira de Souza Neto<sup>1,2,3,4\*</sup>, S. Grousseau<sup>1</sup>, F. Duflo<sup>1</sup>, C. Ducreux<sup>5</sup>, H. Joly<sup>5</sup>, J. Convert<sup>1</sup>, C. Mottolese<sup>6</sup>, F. Dailley<sup>1</sup> and M. Cannesson<sup>7</sup>

<sup>1</sup> Hospices Civils de Lyon, Groupement Hospitalier Est, Hôpital Neurologique Pierre Wertheimer, Service d'Anesthésie Réanimation, 59 boulevard Pinel, 69677 Bron, Cedex, France

<sup>2</sup> CNRS, Laboratoire de Physique, Ecole Normale Supérieure de Lyon, 46, allée d'Italie, 69364 Lyon Cedex 07, France

<sup>3</sup> Hospital Regional, rua José Bongiovani, 1297, CEP 19050-680, Presidente Prudente, São Paulo, Brasil

<sup>4</sup> UNOESTE, rua José Bongiovani, 700, CEP 19050-920, Presidente Prudente, São Paulo, Brasil

<sup>5</sup> Hospices Civils de Lyon, Groupement Hospitalier Est, Hôpital Louis Pradel, Service de Cardiologie C, avenue Doyen Lépine, 69677 Bron, Cedex, France

<sup>6</sup> Hospices Civils de Lyon, Groupement Hospitalier Est, Hôpital Neurologique Pierre Wertheimer, Service de Neurochirurgie Infantile, 59 boulevard Pinel, 69677 Bron, Cedex, France

<sup>7</sup> Department of Anesthesiology and Perioperative Care, University of California Irvine, School of Medicine, Orange, CA, USA

\* Corresponding author. E-mail: edmundopereira-de-souza-neto@chu-lyon.fr

## Editor's key points

- Dynamic predictors are widely used in adult patients.
- Dynamic indices of preload have not been studied extensively in children.
- The study found that pulse pressure variation and plethysmographic waveform variation did not predict fluid responsiveness in children.

**Background.** Dynamic variables are accurate predictors of fluid responsiveness in adults undergoing mechanical ventilation. They can be determined using respiratory variation in aortic flow peak velocity ( $\Delta V_{\text{peak}}$ ), arterial pulse pressure [ $\Delta PP$  and pulse pressure variation (PPV)], or plethysmographic waveform amplitude [ $\Delta POP$  and pleth variability index (PVI)]. These indices have not been validated in children. We studied the ability of these variables to predict fluid responsiveness in mechanically ventilated children.

**Methods.** All results are expressed as median [median absolute deviation (MAD)]. Thirty mechanically ventilated children were studied after undergoing general anaesthesia. Mechanical ventilation was maintained with a tidal volume of 10 ml kg<sup>-1</sup> of body weight.  $\Delta PP$ , PPV,  $\Delta POP$ , PVI,  $\Delta V_{\text{peak}}$ , and aortic velocity–time integral were recorded before and after volume expansion (VE). Patients were considered to be responders to VE when the aortic velocity–time integral increased more than 15% after VE.

**Results.** VE induced significant changes in  $\Delta PP$  [13 (MAD 4) to 9 (5)%], PPV [15 (5) to 9 (5)%],  $\Delta POP$  [15 (10) to 10 (6)%], PVI [13 (6) to 8 (5)%], and  $\Delta V_{\text{peak}}$  [16 (9) to 8 (3)%] ( $P < 0.05$  for all). Differences in  $\Delta PP$ ,  $\Delta POP$ , PPV, and PVI did not reach statistical significance. Only  $\Delta V_{\text{peak}}$  was significantly different between responders (R) and non-responders (NR) to VE [22 (3) vs 7 (1)%, respectively;  $P < 0.001$ ]. The threshold  $\Delta V_{\text{peak}}$  value of 10% allowed discrimination between R and NR.

**Conclusions.** In this study,  $\Delta V_{\text{peak}}$  was the most appropriate variable to predict fluid responsiveness.

**Keywords:** arterial pulse pressure; fluid responsiveness; haemodynamic; plethysmographic waveform; respiratory variations

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Bedside indicators of ventricular preload have been proposed as predictors of fluid responsiveness. The ideal index of fluid responsiveness for clinical use in the operating theatre should be sensitive to changes in loading conditions, predictive of patients' response to volume expansion (VE), reproducible, simple to use, non-invasive, and widely available.<sup>1–4</sup>

No index has been shown to embody all of these characteristics.<sup>1–4</sup> Static indicators such as central venous pressure, pulmonary capillary wedge pressure, or left ventricular end-diastolic area have been shown to be poor predictors of fluid responsiveness.<sup>4–5</sup> Dynamic indices of preload, which reflect ventilation-induced cyclic changes in left ventricular stroke

volume, have been shown to reliably predict the response to fluid administration in adults.<sup>2 4 6 7</sup> During positive pressure ventilation, the inspiratory right ventricular stroke volume decrease is proportional to the degree of hypovolaemia and is transmitted to the left heart after two or three beats (pulmonary vascular transit time).<sup>1 4</sup> Respiratory variations in the arterial pulse pressure ( $\Delta PP$ ) and in the pulse oximetry plethysmographic waveform amplitude ( $\Delta POP$ ) have been extensively studied in mechanically ventilated patients and have been demonstrated to be sensitive to changes in ventricular preload and reliable predictors of fluid responsiveness in adults.<sup>8–12</sup> Recently, Durand and colleagues<sup>13</sup> demonstrated that  $\Delta PP$  is of little value for fluid responsiveness prediction in severely ill children. However, little is known about the ability of these indices to predict fluid responsiveness in children undergoing surgery. Durand and colleagues<sup>13</sup> suggested that the poor predictive value of  $\Delta PP$  in this setting may be related to a high vascular compliance in children. However, the plethysmographic waveform is not a pressure signal but a volumetric signal and thus may be less impacted by vascular compliances observed in the paediatric setting.

The aims of this study were (i) to test the ability of  $\Delta PP$  and  $\Delta POP$  to predict fluid responsiveness in children under general anaesthesia and mechanical ventilation, and (ii) to explore the ability of respiratory variations in aortic flow peak velocity to predict fluid responsiveness in this setting.

## Methods

This study was approved by the local Ethics Committee and was conducted in accordance with the Declaration of Helsinki (2000) of the World Medical Association. The protocol was approved by the ethical committee of our institution (CPP, Hospices Civils de Lyon). After explanation of the experimental procedure, written and informed parental consent was obtained before operation for all patients. There were two age strata in this study: 0–6 yr (defined to be from birth to the day before the sixth birthday) and 6–14 yr (i.e. from the sixth birthday to the day before the 15th birthday).

We studied mechanically ventilated children referred for neurosurgery immediately after induction of general anaesthesia and before incision. The anaesthetic management of all patients followed a standard procedure. After anaesthetic induction (6.0% sevoflurane and remifentanyl i.v.  $0.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ ), the trachea was intubated and mechanical ventilation was started. Anaesthesia was maintained with sevoflurane 1 minimal alveolar concentration in  $\text{O}_2/\text{N}_2\text{O}$  (50%/50%) associated with i.v. remifentanyl ( $0.25 \mu\text{g kg}^{-1} \text{min}^{-1}$ ). All patients were ventilated in a volume-controlled mode with a tidal volume of  $10 \text{ ml kg}^{-1}$  of body weight at a frequency adapted to age. Positive end-expiratory pressure was set between 0 and  $2 \text{ cm H}_2\text{O}$ .

After induction of anaesthesia, an Angiocath<sup>TM</sup> (Becton Dickinson, Franklin Lakes, NJ, USA) was inserted in the radial artery for arterial pressure continuous measurement and recording. Pressure transducers (Medex<sup>TM</sup> Medical Ltd, Rossendale, Lancashire, UK) were placed on the mid-axillary

line and fixed to the operation table in order to keep the transducer at the atrial level during the entire protocol. All transducers were zeroed to atmospheric pressure before each step of the protocol. A pulse oximeter probe (Oxymax<sup>TM</sup>, Tyco Healthcare Group LP, Pleasanton, CA, USA) was attached to the index finger of either the right or the left hand and was wrapped to prevent outside light from interfering with the signal. The children were connected to a Philips monitor (IntelliVue MP70<sup>TM</sup>, Philips Medical Systems, Suresnes, France), and all haemodynamic variables were recorded and transferred at each step of the protocol from the Philips monitor to a personal computer using data acquisition software (TrendfaceSolo 1.1<sup>TM</sup>, Ixellence GmbH, Wildau, Germany).

Systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, and heart rate (HR) were recorded before and after a VE with  $20 \text{ ml kg}^{-1}$  of normal saline over 15 min.

## Calculation of respiratory variations in arterial pulse pressure

PP was defined as the difference between systolic and diastolic pressure. Maximal ( $PP_{\text{max}}$ ) and minimal ( $PP_{\text{min}}$ ) values were determined over the same respiratory cycle.  $\Delta PP$  was then calculated manually as previously described:<sup>14</sup>  $\Delta PP = (PP_{\text{max}} - PP_{\text{min}}) / [(PP_{\text{max}} + PP_{\text{min}}) / 2]$ . The measurements were repeated on three consecutive respiratory cycles and averaged for statistical analysis.

PP variation (PPV) was determined automatically by a commercially available algorithm which has been described previously.<sup>15 16</sup> Algorithm-derived PPV is displayed online in real time by Philips IntelliVue MP70 monitors. Briefly, it allows for automatic PP determination from the arterial pressure waveform alone with no need for the airway pressure acquisition. This method is based on automatic detection algorithms, kernel smoothing, and rank-order filters.<sup>15</sup> PPV was calculated and averaged over four cycles of 8 s. The  $\Delta PP$  and PPV were recorded before and after VE.

## Assessment of the respiratory variations in POP waveform amplitude analysis

A pulse oximeter probe (LNOP<sup>®</sup>, Masimo Corporation, Irvine, CA, USA) was placed on the index finger of one hand, wrapped to prevent outside light from interfering with the signal, and connected to a Masimo Radical 7<sup>TM</sup> monitor (Masimo Corporation) with pleth variability index (PVI) software (version 7.0.3.3 [EC]). Another pulse oximeter probe (Oxymax<sup>TM</sup>, Tyco Healthcare Group LP) was attached to the third finger. POP waveforms from this pulse oximeter were recorded from the IntelliVue MP70 monitor (IntelliVue MP70; Philips Medical Systems) and transferred to a personal computer using data acquisition software (TrendfaceSolo 1.1; Ixellence GmbH) and were analysed by an observer blinded to the remaining haemodynamic data.

The plethysmographic gain factor was held constant during the recording of POP waveforms, so that the POP waveform amplitude did not depend on automatic gain adjustment. POP waveform amplitude was measured

manually on a beat-to-beat basis as the vertical distance between the peak and the preceding trough in the waveform and was expressed in number of pixels. Maximum (POP<sub>max</sub>) and minimum POP (POP<sub>min</sub>) were determined over the same respiratory cycle.  $\Delta$ POP was then calculated as previously described:<sup>8</sup>  $POP = (POP_{max} - POP_{min}) / [(POP_{max} + POP_{min}) / 2]$ . The measurements were obtained after three consecutive respiratory cycles and averaged for statistical analysis. The  $\Delta$ POP was recorded before and after the VE with 20 ml kg<sup>-1</sup> of normal saline over 15 min.

### PVI calculation

PVI is an automatic measure of the dynamic change in perfusion index (PI) that occurs during a complete respiratory cycle. Pulse oximetry uses red and infrared light. A constant amount of light (DC) from the pulse oximeter is absorbed by the skin, other tissues, and non-pulsatile blood, whereas a variable amount of light (AC) is absorbed by the pulsating arterial inflow. For PI calculation, the infrared pulsatile signal is indexed against the non-pulsatile infrared signal and expressed as a percentage [ $PI = (AC/DC) \times 100$ ], reflecting the amplitude of the pulse oximeter waveform. The PVI calculation  $\{PVI = [(PI_{max} - PI_{min}) / PI_{max}] \times 100\}$  measures changes in PI over a time interval sufficient to include one or more complete respiratory cycles and is displayed continuously.<sup>9,12</sup> The PVI value was recorded before and after the VE with 20 ml kg<sup>-1</sup> of normal saline over 15 min (Masimo Radical 7™, Masimo Corporation).

We recorded both manual and automatic calculations of measurements to present similar methodologies for respiratory variations in arterial pulse pressure and pulse oximeter waveform amplitude recordings (i.e.  $\Delta$ PP and PPV vs  $\Delta$ POP and PVI).

### Echocardiography analyses

Transthoracic cardiac echography was performed using a Siemens Acuson X300™ (Erlangen, Germany). Measurements were made by one investigator (E.P.S.N.) and analysed later by two investigators blinded for the haemodynamic data (C.D. and H.J.). Pulsed Doppler aortic flow was recorded at the exact level of the annulus from the apical five-chamber view. The aortic velocity–time integral (VTI<sub>ao</sub>) was measured as the mean of three to five consecutive measurements over a single respiratory cycle. Patients showing an increase in VTI<sub>ao</sub> of 15% or more, after VE, were classified as responders (R). Patients whose VTI<sub>ao</sub> increased by <15% were classified as non-responders (NR).

We calculated  $\Delta$ Vpeak as previously described by Feissel and colleagues<sup>17</sup> in order to assess the respiratory variations in aortic flow peak velocity to compare it with  $\Delta$ PP and  $\Delta$ POP.  $\Delta Vpeak = (Vpeak_{max} - Vpeak_{min}) / [(Vpeak_{max} + Vpeak_{min}) / 2]$ , where Vpeak<sub>max</sub> and Vpeak<sub>min</sub> are the maximum and minimum aortic flow peak velocities over a single respiratory cycle, respectively.

Additionally, digital routine grey-scale two-dimensional cine loops from three consecutive beats were obtained at

end-expiratory apnoea from the mid-left ventricular short-axis view at depths of 5–19 cm. Mid-left ventricular short-axis views were selected for left ventricular end-diastolic area (LVEDA) measurement with the papillary muscle as a consistent internal anatomical landmark.

VTI<sub>ao</sub>, LVEDA, and  $\Delta$ Vpeak were recorded before and after a VE (20 ml kg<sup>-1</sup> of normal saline over 15 min).

### Statistical analysis

The Mann–Whitney test was used to compare patient characteristics (age, weight, and body mass index) and haemodynamic and respiratory data between groups.

The effects of VE on haemodynamic variables were assessed using a non-parametric Wilcoxon rank-sum test within each group of patients. A Fisher exact test was performed to compare nominal data. Receiver-operating characteristic (ROC) curves were generated for  $\Delta$ PP, PPV,  $\Delta$ POP, and PVI, and areas under the ROC curves were calculated and compared (MedCalc 8.0.2.0; MedCalc Software, Mariakerke, Belgium). Power analysis showed that 25 patients were necessary to detect a difference of 0.15 between POP and PVI areas under the ROC curves (5% type I error rate, 80% power, two-tailed test). All results are expressed as median [median absolute deviation (MAD)] except age which is expressed as median and range. The median absolute deviation is a variation of the average absolute deviation that is even less affected by outlying values because these values have less influence on the calculation of the median than they do on the mean. In general, for data with extreme values, the median absolute deviation or inter-quartile range can provide a more stable estimate or variability than the standard deviation.

Inter-observer agreement regarding respiratory variations in aortic flow peak velocity ( $\Delta$ Vpeak) and the aortic velocity–time integral (VTI<sub>ao</sub>) was assessed with the intraclass correlation coefficient (ICC). The mean bias was calculated using 1–ICC.

P-values lower than a 0.05 chosen level are regarded as statistically significant. All statistical analyses are performed using the StatView™ software for Windows (version 4.57, Abacus Concepts Inc., Berkeley, CA, USA).

## Results

### Patient characteristics

There were 19 patients in the 0–6 age group [median age 2 (1.6) yr old ranging from 5.5 months to 5 yr, median weight 11 (2) kg, median height 83 (15) cm, nine females, 16 craniostenosis, three posterior fossa tumours] and 11 patients in the 6–14 age group [median age 11 (3) yr old ranging from 6 to 14 yr, median weight 32 (8) kg, median height 147 (11) cm, six females, 11 posterior fossa tumours].

No patients received vasoactive drugs. Peak airway pressure was 17 (5) cm H<sub>2</sub>O and mean ventilatory frequency/HR ratio was 4.3 (0.8). This ratio was above 3.6 in every patient.

## Changes in haemodynamic and respiratory variables after VE

Haemodynamic and echocardiography data before and after VE in R and NR from the 0–6 age group and the 6–14 age group can be seen in Tables 1 to 4. The mean bias of the inter-observer agreement was 0.2 (3.5)% for respiratory variations in aortic flow peak velocity ( $\Delta V_{\text{peak}}$ ) and 0.19 (4)% for the aortic velocity–time integral ( $VTI_{\text{ao}}$ ).

Respiratory variations in arterial pulse pressure and in plethysmographic waveform amplitude before and after VE in R and NR from the 0–6 age group and the 6–14 age group can be seen in Tables 2 and 4. The pulse oximeter plethysmography available was analysable in all patients. The PI was above 6% in both groups. The PVI was displayed for all patients, no matter the PI value. Peak airway pressure was unchanged during the study protocol.

In the 0–6 age group (Tables 1 and 2), VE induced a statistically significant increase ( $\sim 42\%$ ) in  $VTI_{\text{ao}}$  only in R. At the same time, we observed statistically significant decreases in R and NR for  $\Delta\text{POP}$  ( $-60\%$  in R and  $-64\%$  in NR) and PPV ( $-54\%$  in R and  $-58\%$  in NR); and significant decreases only in R for PVI ( $-50\%$ ),  $\Delta\text{PP}$  ( $-50\%$ ) and  $\Delta V_{\text{peak}}$  ( $-41\%$ ).

In the 6–14 age group (Tables 3 and 4), VE induced a statistically significant increase in  $VTI_{\text{ao}}$  ( $\sim 27\%$ ) and a decrease in HR ( $\sim 11\%$ ) only in R. At the same time, we observed statistically significant decreases in R for  $\Delta\text{POP}$  ( $-47\%$ ), PVI ( $-40\%$ ),  $\Delta\text{PP}$  ( $-25\%$ ), PPV ( $-47\%$ ), and  $\Delta V_{\text{peak}}$  ( $-59\%$ ).

$\Delta V_{\text{peak}}$  before and after VE was significantly lower in NR compared with R in both groups (Tables 2 and 4, and Fig. 1).

The area under the ROC curve for all variables can be seen in Figure 2. In the 0–6 age group, the area under the ROC curve (95% confidence interval) for all variables was: for  $\Delta V_{\text{peak}}$  1.0 (0.82–1.00), for  $\Delta\text{POP}$  0.51 (0.28–0.74), for PVI 0.63 (0.38–0.84), for  $\Delta\text{PP}$  0.71 (0.47–0.89), for PPV 0.52 (0.29–0.76), and for LVEDA 0.59 (0.35–0.81). In the 6–14 age group, the area under the ROC curve (95% confidence interval) for all variables was: for  $\Delta V_{\text{peak}}$  1.0 (0.73–1.00),

**Table 1** Haemodynamic and echocardiography data before and after VE in R and NR from the 0–6 age group. Values are expressed as median (MAD). DAP, diastolic arterial pressure; HR, heart rate; MAP, mean arterial pressure; LVEDA, left ventricular end-diastolic area; SAP, systolic arterial pressure;  $VTI_{\text{ao}}$ , aortic velocity–time integral (cf. Echocardiography analyses section). \*Non-parametric Mann–Whitney test:  $P < 0.05$  vs R. †Non-parametric Wilcoxon test:  $P < 0.05$  vs before VE

	Responders (n=10)		Non-responders (n=9)	
	Before VE	After VE	Before VE	After VE
HR (beats min <sup>-1</sup> )	103 (MAD12)	101 (19)	90 (7)	91 (10)
SAP (mm Hg)	71 (5)	73 (5)	70 (4)	79 (9)
DAP (mm Hg)	44 (4)	45 (6)	44 (1)	43 (3)
MAP (mm Hg)	54 (6)	55 (6)	53 (1)	53 (4)
LVEDA(cm <sup>2</sup> m <sup>-2</sup> )	4.2 (0.5)	4.5 (0.5)	4.0 (0.3)	4.1 (0.4)
$VTI_{\text{ao}}$ (cm)	12 (1)	17 (1) <sup>†</sup>	16 (1)*	17 (0.4)

**Table 2** Respiratory variations in arterial pulse pressure and in plethysmographic waveform amplitude before and after VE in R and NR from the 0–6 age group. Values are expressed as median (MAD).  $\Delta\text{POP}$ , respiratory variations in plethysmographic waveform amplitude; PVI, pleth variability index;  $\Delta\text{PP}$ , respiratory variations in arterial pulse pressure; PPV, automated pulse pressure variations;  $\Delta V_{\text{peak}}$ , respiratory variations in aortic velocity–time integral. \*Non-parametric Mann–Whitney test:  $P < 0.05$  vs R. †Non-parametric Wilcoxon test:  $P < 0.05$  vs before VE

	Responders (n=10)		Non-responders (n=9)	
	Before VE	After VE	Before VE	After VE
$\Delta\text{POP}$ (%)	15 (MAD 4)	6 (1) <sup>†</sup>	11 (3)	7 (2) <sup>†</sup>
PVI (%)	10 (3)	5 (2) <sup>†</sup>	8 (2)	8 (2)
$\Delta\text{PP}$ (%)	12 (2)	6 (2) <sup>†</sup>	11 (2)	9 (2)
PPV (%)	13 (3)	7 (1) <sup>†</sup>	12 (2)	7 (1) <sup>†</sup>
$\Delta V_{\text{peak}}$ (%)	22 (3)	9 (2) <sup>†</sup>	7 (2)*	6 (2)*

**Table 3** Haemodynamic and echocardiography data before and after VE in R and NR from the 6–14 age group. Values are expressed as median (MAD). DAP, diastolic arterial pressure; HR, heart rate; MAP, mean arterial pressure; LVEDA, left ventricular end-diastolic area; SAP, systolic arterial pressure;  $VTI_{\text{ao}}$ , aortic velocity–time integral (cf. Echocardiography analyses section). \*Non-parametric Mann–Whitney test:  $P < 0.05$  vs R. †Non-parametric Wilcoxon test:  $P < 0.05$  vs before VE

	Responders (n=7)		Non-responders (n=4)	
	Before VE	After VE	Before VE	After VE
HR (beats min <sup>-1</sup> )	72 (MAD 10)	64 (9) <sup>†</sup>	80 (8)	71 (6)
SAP (mm Hg)	78 (2)	88 (5)	81 (3)	78 (4)
DAP (mm Hg)	54 (7)	58 (5)	52 (2)	48 (3)
MAP (mm Hg)	63 (6)	69 (3)	62 (0)	58 (2)
LVEDA(cm <sup>2</sup> m <sup>-2</sup> )	5.6 (0.5)	5.3 (0.4)	5.8 (0.4)	6.1 (0.7)
$VTI_{\text{ao}}$ (cm)	15 (1)	19 (0.9) <sup>†</sup>	17 (5)	16 (5)

**Table 4** Respiratory variations in arterial pulse pressure and in plethysmographic waveform amplitude before and after VE in R and NR from the 6–14 age group. Values are expressed as median (MAD).  $\Delta\text{POP}$ , respiratory variations in plethysmographic waveform amplitude; PVI, pleth variability index;  $\Delta\text{PP}$ , respiratory variations in arterial pulse pressure; PPV, automated pulse pressure variations;  $\Delta V_{\text{peak}}$ , respiratory variations in aortic velocity–time integral. \*Non-parametric Mann–Whitney test:  $P < 0.05$  vs R. †Non-parametric Wilcoxon test:  $P < 0.05$  vs before VE

	Responders (n=7)		Non-responders (n=4)	
	Before VE	After VE	Before VE	After VE
$\Delta\text{POP}$ (%)	15 (MAD 4)	7 (2) <sup>†</sup>	10 (2)	10 (2)
PVI (%)	15 (2)	9 (4) <sup>†</sup>	12 (5)	8 (3)
$\Delta\text{PP}$ (%)	12 (2)	9 (2) <sup>†</sup>	12 (1)	12 (4)
PPV (%)	19 (4)	10 (2) <sup>†</sup>	14 (5)	11 (4)
$\Delta V_{\text{peak}}$ (%)	22 (3)	9 (1) <sup>†</sup>	5 (2)*	5 (1)*



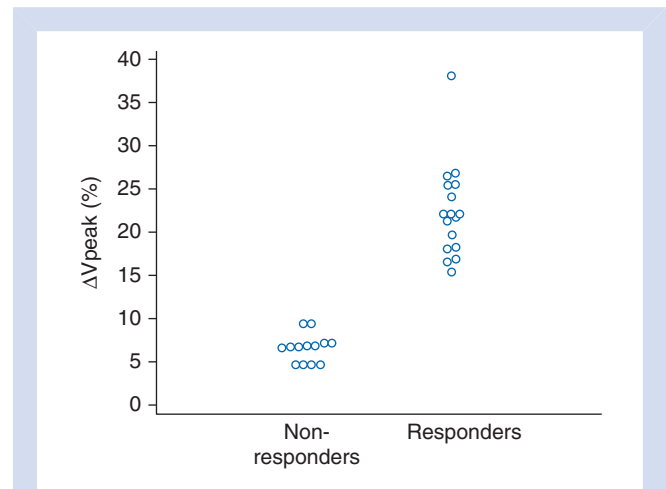
for  $\Delta$ POP 0.57 (0.27–0.84), for PVI 0.54 (0.24–0.82), for  $\Delta$ PP 0.60 (0.29–0.86), for PPV 0.60 (0.29–0.86), and for LVEDA 0.71 (0.39–0.93). For the pair-wise comparison of ROC curves,  $\Delta$ Vpeak was better than all other recorded values in discriminating between R and NR (Fig. 3). The threshold  $\Delta$ Vpeak value of 10% allowed discrimination between R and NR with a sensitivity (95% confidence interval) of 100% (81–100%) and a specificity (95% confidence interval) of 100% (75–100%). As with the 0–6 age group, in the 6–14 age group's pair-wise comparison of ROC curves,  $\Delta$ Vpeak was better than all the other variables in discriminating between R and NR (Fig. 3). Because HR was higher in R than in NR to VE (even if this difference did not reach statistical significance), we tested the ability of HR to predict fluid responsiveness since it may act as a confounding factor. We found no ability of this parameter to predict fluid responsiveness in the global population [area under the curve is 0.50 (95% confidence interval 0.31–0.69);  $P=1.00$ ] and in subgroups [0–6 yr old: area under the curve is 0.62 (0.38–0.82);  $P=0.37$ , and 6–14 yr old: area under the curve is 0.66 (0.32–0.92);  $P=0.38$ ].

From the results presented above for both groups, we found that although  $\Delta$ Vpeak was an accurate predictor of fluid responsiveness, no arterial pressure- nor plethysmographic-derived variable was accurate in predicting fluid responsiveness. For both age groups, we observed statistically significant relationships between  $\Delta$ PP and PPV ( $r=0.74$ ;  $P<0.001$ ),  $\Delta$ POP and PVI ( $r=0.39$ ;  $P<0.05$ ),  $\Delta$ PP and  $\Delta$ POP ( $r=0.48$ ;  $P<0.001$ ), and PPV and PVI ( $r=0.78$ ;  $P<0.001$ ). However, we found no significant relationship between  $\Delta$ Vpeak and  $\Delta$ PP ( $r=0.37$ ;  $P=0.05$ ),  $\Delta$ Vpeak and PPV ( $r=0.01$ ;  $P=0.51$ ),  $\Delta$ Vpeak and  $\Delta$ POP ( $r=0.01$ ;  $P=0.78$ ), or  $\Delta$ Vpeak and PVI ( $r=0.01$ ;  $P=0.40$ ).

## Discussion

The present study shows that invasive and non-invasive dynamic variables derived from the arterial pressure and from the plethysmographic waveforms cannot predict response to VE in children under general anaesthesia and mechanical ventilation in the operating theatre. However, respiratory variations in the aortic flow peak velocity are able to predict fluid responsiveness in this setting.

Fluid responsiveness assessment is a daily challenge in children undergoing surgery and in the intensive care unit. Moreover, prediction of fluid responsiveness (defined as a significant increase in cardiac output after expansion) is difficult. Preload variables, such as central venous pressure or LVEDA, are invasive or operator-dependent and have been shown to be poor predictors of fluid responsiveness.<sup>5 17</sup> Consequently, dynamic variables may be of interest in this setting. In the anaesthesiology setting, cardiopulmonary interactions have been used as a surrogate to assess the effects of a fluid challenge on stroke volume.<sup>4</sup> In patients under general anaesthesia, positive pressure ventilation induces cyclic changes in vena cava blood flow, pulmonary artery flow, and aortic blood flow. During inspiration, vena

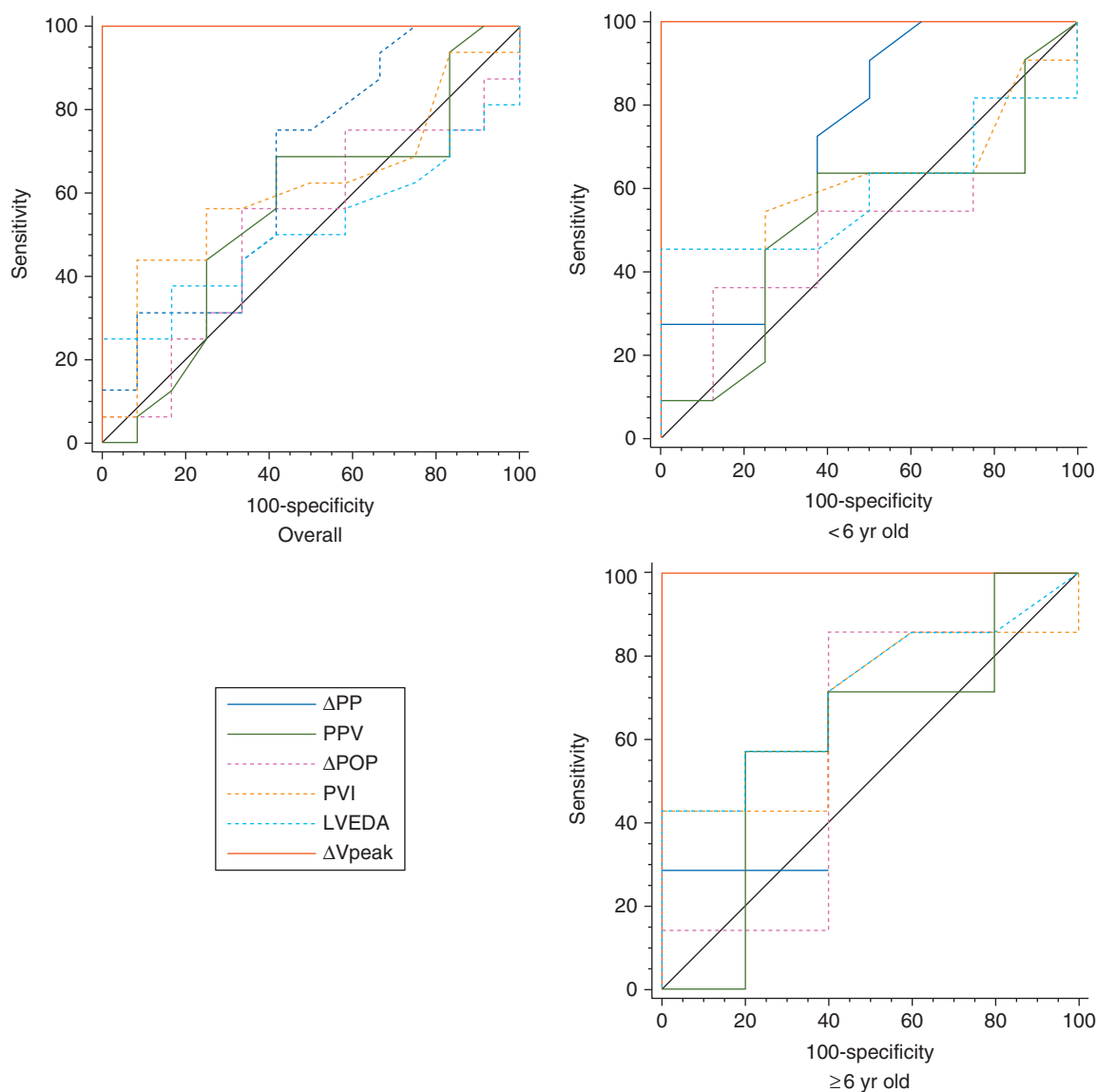


**Fig 1** Individual values of respiratory variations in peak aortic velocity in R and NR to VE.  $\Delta$ Vpeak, respiratory variations in aortic flow peak velocity.

cava blood flow decreases (venous return decreases) and, according to the Frank–Starling relationship, pulmonary artery flow decreases.<sup>4</sup> Approximately three beats later, this decrease in pulmonary artery flow is transmitted to the left ventricle, inducing a decrease in aortic stroke volume. Consequently, mechanically ventilated patients under general anaesthesia present with cyclic changes in left ventricular stroke volume. These respiratory variations in left ventricular stroke volume or its surrogates (arterial pressure waveform and plethysmographic waveform) have consistently been shown to be predictive of response to VE in adults and have recently been proposed for goal-directed haemodynamic optimization during anaesthesia.<sup>3 4 8 18</sup>

In the present study, we tested the ability of these variables to predict fluid responsiveness in paediatric patients under general anaesthesia and mechanical ventilation in the operating theatre.

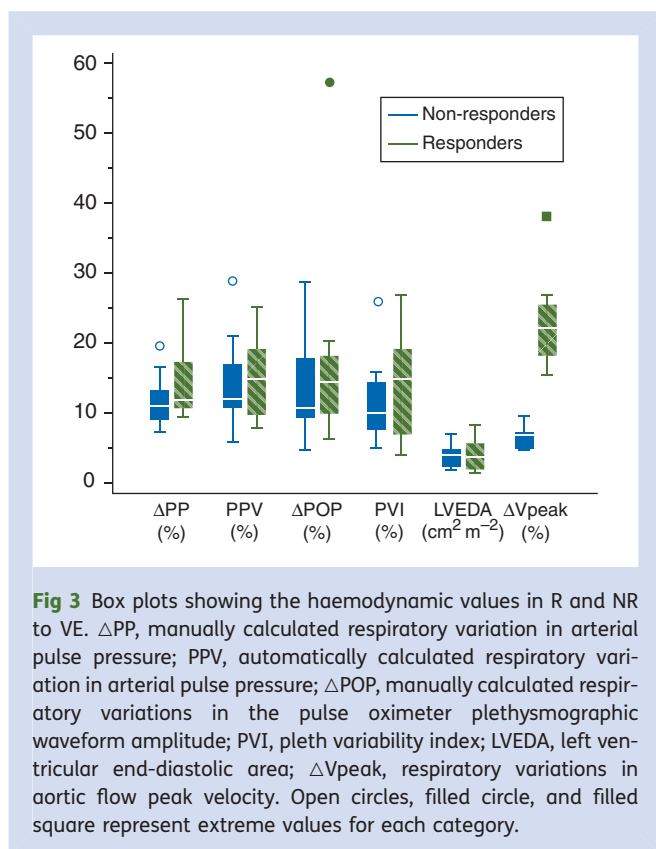
It is our unit policy and it was stated to administrate an initial VE of around 20 ml kg<sup>-1</sup> as fluid management strategies for the neurosurgery procedure like craniostenosis and posterior fossa tumours.<sup>19</sup> Moreover, this VE was also used by Durand and colleagues<sup>13</sup> to evaluate whether respiratory variations in aortic blood flow could predict fluid responsiveness. Durand and colleagues<sup>13</sup> studied the ability of  $\Delta$ PP, systolic pressure variations, and  $\Delta$ Vpeak to predict fluid responsiveness in children in the intensive care unit. They found that neither  $\Delta$ PP nor systolic pressure variations were predictive while  $\Delta$ Vpeak was. They concluded that arterial pressure waveform-derived variables were not predictive because they were impacted by the arterial compliance of children that may have absorbed and nullified the respiratory variations observed in left ventricular stroke volume.<sup>13</sup> In our study, we hypothesized that the plethysmographic waveform would be able to bypass this limitation since the plethysmographic waveform relies on light absorption that is proportional to the



**Fig 2** The area under the ROC curve for all variables. In the 0–6 age group, the area under the ROC curve (95% confidence interval) for all variables was: for  $\Delta V_{peak}$  1.0 (0.82–1.00), for  $\Delta POP$  0.51 (0.28–0.74), for PVI 0.63 (0.38–0.84), for  $\Delta PP$  0.71 (0.47–0.89), for PPV 0.52 (0.29–0.76) and for LVEDA 0.59 (0.35–0.81). In the 6–14 age group the area under the ROC curve (95% confidence interval) for all variables was: for  $\Delta V_{peak}$  1.0 (0.73–1.00), for  $\Delta POP$  0.57 (0.27–0.84), for PVI 0.54 (0.24–0.82), for  $\Delta PP$  0.60 (0.29–0.86), for PPV 0.60 (0.29–0.86), and for LVEDA 0.71 (0.39–0.93).  $\Delta PP$ , manually calculated respiratory variation in arterial pulse pressure; PPV, automatically calculated respiratory variation in arterial pulse pressure;  $\Delta POP$ , manually calculated respiratory variations in the pulse oximeter plethysmographic waveform amplitude; PVI, pleth variability index; LVEDA, left ventricular end-diastolic area;  $\Delta V_{peak}$ , respiratory variations in aortic flow peak velocity.

volume of blood in the tissue where it is recorded rather than on the arterial pressure itself.<sup>20–21</sup> However, our results did not find any ability of plethysmographic-derived variables to predict fluid responsiveness and thus confirm the findings of Durand and colleagues in the anaesthesiology setting, that is, stroke volume variations (SVV) alone predict fluid responsiveness. We believe that these results are of importance since they confirm that despite the fact that respiratory variations in left ventricular stroke volume exist and are accurate predictors, peripheral

variables (derived from the arterial pressure and the plethysmographic waveforms) are not. Thus, it is more likely that the inability of  $\Delta PP$  and  $\Delta POP$  to predict fluid responsiveness is related to vascular compliance rather than lung compliance, thoracic compliance, or both. As stated by others, changes of resistive, inertial, and viscoelastic properties appear functional in controlling the ratio of pulsatile power to active power and keeping arterial efficiency as high as 97% in infants and children.<sup>22–24</sup> Senzaki and colleagues<sup>24</sup> demonstrated that both



peripheral and proximal arterial wall distensibility in children decline after birth. The value of the arterial compliance/body surface area ratio (arterial compliance normalized to body surface area to eliminate factors associated with development of arterial size) significantly decreased with age and declined fastest during the first several years of life, suggesting that there is an increase in arterial wall stiffness with increasing age in children.<sup>22–24</sup>

Several articles have studied the age-associated changes in pulsatile component properties of the arterial system.<sup>22–24–27</sup> The aortic wall in humans contains elastin, collagen, vascular smooth muscle cells, and proteoglycans.<sup>26–28</sup> Aged arteries are known to show more stiffness than young arteries. However, the age when arterial properties in children become similar to those observed in adults is not known.<sup>22–26–28</sup> Avolio and colleagues<sup>25</sup> demonstrated a non-linear increase in pulse wave velocity in arteries of the arms and legs, a peripheral arterial system. The increase in pulse wave velocity in the arms and legs was greater in subjects under 10 yr of age than that in subjects over 10 yr of age. This finding is consistent with the present observation of non-linear increase in arterial stiffness represented by arterial compliance/body surface area, which conveys information about the total arterial system, including peripheral arteries. In the human iliac artery, Roach and Burton<sup>26</sup> demonstrated that changes in arterial compliance observed until the age of 20 yr old are mainly related to wall thickness augmentation,

whereas after this age, changes in arterial compliance are more related to elastic arterial tissue changes. This difference between children and adults may explain why  $\Delta$ PP and PPV did not predict fluid responsiveness in children between 6 and 14 yr of age.

Because our study was conducted in patients with healthy lungs at baseline, one may have hypothesized that mechanical ventilation may not be able to induce enough changes in pressure to induce cyclic changes in left ventricular stroke volume. Lung compliance changes with age and the amount of surfactant, alveolar structure, and elastic tissue in the lung.<sup>29</sup> The compliance and elastic properties of the chest wall reflect chest wall configuration, rib ossification, tension of the diaphragm, abdominal musculature, and intra-abdominal pressure.<sup>29–30</sup> In healthy adults, the relaxation volume of the respiratory system is dictated by the balance of forces between the inward elastic recoil pressure of the lung and the outward recoil pressure of the chest wall.<sup>30</sup> In infants, outward recoil of the thorax is extremely low (compliance is high) because of the soft cartilaginous rib cage and the poorly developed thoracic musculature.<sup>30</sup> In comparison, inward recoil of the lung in infants is only mildly diminished when compared with inward recoil of adults. However, because  $\Delta$ Vpeak was predictive of fluid responsiveness while  $\Delta$ PP and  $\Delta$ POP were not, this hypothesis can be ruled out.

In addition to the classical  $\Delta$ PP and  $\Delta$ POP variables, we studied automated and continuous variables (PPV and PVI). All four indices were not predictive of fluid responsiveness. However, both PPV algorithms implemented on the Philips IntelliVue MP70 monitor<sup>15–16</sup> and PVI<sup>9</sup> monitor the respiratory variations in the arterial pulse pressure and in the PI (and can be considered as a surrogate for the amplitude of the plethysmographic waveform). Other algorithms and software allow for the assessment of stroke volume and of SVV using a more complex analysis of the arterial pressure waveform. This is the case for the Vigileo-FloTrac monitor,<sup>31</sup> the PiCCO system,<sup>6</sup> and the LiDCO system. However, the Vigileo-FloTrac monitor is not designed for children, and the SVV and PPV algorithms from the LiDCO device have not been tested in paediatric patients. Renner and colleagues<sup>32</sup> studied the PPV and SVV algorithms from the PiCCO device in paediatric porcine model.<sup>33–34</sup> Interestingly, they found that these variables were sensitive to changes in ventricular preload but that SVV was superior to PPV in predicting fluid responsiveness. These data have not been validated in clinical practice. Thus, whether SVV assessed through arterial pressure waveform analysis can predict fluid responsiveness requires further investigations.

Finally, in our study, aortic velocity–time integral variations were evaluated using  $\Delta$ Vpeak. This may not be practical in the clinical setting since it requires the use of transoesophageal echocardiography in order to obtain intraoperative data. In adults, limitations of dynamic variables of fluid responsiveness relying on cardiopulmonary interactions can be overcome using passive leg raising.<sup>35</sup> In the paediatric population, this manoeuvre may not be applicable since the volume of blood shifted from the lower limbs

to the thorax may dramatically vary from one patient to the other depending on the age of the patient and on the ratio between the legs and the thorax. Consequently, other tests such as end-expiratory occlusion may be of interest in this setting and require further investigation.<sup>36</sup>

### Study limitations

Our study has several limitations. First,  $\Delta$ POP and PVI were recorded in the finger. It is now known that these variations depend on the site of measurements. For example, the POP waveform can be up to 10 times stronger in the head when compared with the finger.<sup>37</sup> Further studies evaluating the ear, forehead, and finger signal for fluid responsiveness prediction in the current setting may be of interest. Secondly, even if  $\Delta$ Vpeak was predictive in our study, one has to remember that this variable may be affected by arrhythmias, spontaneous breathing, open chest conditions, the tidal volume, and the HR/ventilatory frequency ratio. Thirdly, we found a threshold value of 10% for  $\Delta$ Vpeak. This threshold is supposed to provide acceptable sensitivity and specificity for fluid responsiveness prediction. However, clinical practice is not a 'black or white' setting and one must keep in mind that there is a probable grey zone around this single threshold value. Moreover, even if the area under the ROC curve and sensitivity and specificity are very high for  $\Delta$ Vpeak, its predictive value has a comparatively wide 95% confidence interval (from 0.824 to 1.000 in the 0–6 age and 0.735 to 1.000 in the 6–14 age group). A lower predictive value might be found in a different setting. Finally, we did not study systolic pressure variation or its  $\Delta$ up and  $\Delta$ down components. These indices may have a better predictive value. However, most studies focusing on this topic have shown that  $\Delta$ PP was the best predictor of fluid responsiveness and was superior to systolic pressure variation.<sup>14</sup>

In conclusion, our results show that invasive and non-invasive dynamic variables derived from the arterial pressure ( $\Delta$ PP and PPV) and the plethysmographic waveforms ( $\Delta$ POP and PVI) do not predict response to VE in children under general anaesthesia and mechanical ventilation in the operating theatre. However, respiratory variations in the aortic flow peak velocity ( $\Delta$ Vpeak) were shown to be most appropriate for prediction of fluid responsiveness in this setting.

### Conflict of interest

M.C. is a consultant for Masimo Corporation, Edwards Lifesciences, and Covidien.

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