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PEDIATRIC ORIGINAL

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Predicting fluid responsiveness in 100 critically ill children: the effect of baseline contractility

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Take-home message: The majority of advanced haemodynamic variables (volumetric and dynamic) have poor to moderate predictive ability in children in terms of the stroke volume response to fluid boluses. Baseline contractility is an important factor influencing patients' response to fluid volume loading, such that a patient with poor baseline contractility will need to increase their end-diastolic volume by an increment that is 3–4 times greater than that of a patient with good contractility to be able to increase stroke volume by more than 15 %.

Electronic supplementary material
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Abstract *Purpose:* Fluid overload is a risk factor for poor outcome in intensive care; thus volume loading should be tailored towards patients who are likely to increase stroke volume. We aimed to evaluate the paediatric predictive ability (stroke volume increase of at least 15 % after fluid bolus) of novel and established volumetric and dynamic haemodynamic variables, and assess the influence of baseline contractility on response. *Methods:* We assessed 142 volume loading episodes (10 ml/kg crystalloid) in 100 critically ill ventilated children, median (interquartile) weight 10 (5.6–15) kg. Eight advanced haemodynamic variables were assessed using two commercially available devices. Systemic ventricular contractility was measured as the maximum rate of systolic arterial pressure rise. *Results:* Overall, predictive ability was poor, with volumetric variables performing better than dynamic (area under receiver operating characteristic curves ranged from 0.53 to 0.67). The best predictor was total end-diastolic volume index; however, this did not increase in a consistent way with volume loading, with change post volume being weakly related to baseline values ($r = -0.19$, $p = 0.02$). A multivariable model quantified the importance of contractility in stroke volume response. Children with high baseline contractility (≥75th centile) typically achieved a positive stroke volume response when end-diastolic volume values changed by 10–15 ml/m$^{2.6}$, whereas patients with low contractility (≤25th centile) typically required end-diastolic volume increases of 35–40 ml/m$^{2.6}$. *Conclusions:* Current paediatric predictors of volume response perform poorly; prediction may be improved if baseline contractility is taken into account.

Keywords Cardiac output · Fluid responsiveness · Contractility · Paediatric

Introduction

Fluid resuscitation may increase cardiac stroke volume in critically ill patients with suboptimal preload [1]. However, this carries risk, as overzealous fluid administration can lead to fluid overload with deleterious consequences on patient outcome [2–4]. Approximately 40–60 % of patients will typically respond to fluid therapy, by increasing cardiac output by more than 10–15 % [5, 6]. Thus, the ability to predict which patients will respond may obviate the need for unnecessary fluid administration.

The past two decades have witnessed development of several haemodynamic variables aimed at predicting fluid responsiveness [1, 5–9]. Broadly speaking, these are classified as static and dynamic. Static variables are typically volumetric and estimate either (1) maximal ventricular volumes, found at end-diastole, or (2) an aspect of intravascular volume; both are commonly derived using indicator dilution techniques [10]. Dynamic variables rely on the principle that cyclical changes in preload occur during the ventilatory cycle, which translate into changes in stroke volume via the Frank–Starling mechanism: the greater the change, the higher the likelihood of volume response.

Early enthusiasm for the predictive ability of these variables has been tempered by later studies, which show a poorer performance when applied in normal clinical practice [11–13]. This is likely for a variety of reasons, including low tidal volume ventilation, spontaneous respirations, arrhythmias, and heart valve regurgitation [11–13]. However, two other haemodynamic factors which can compromise predictive ability require consideration. First, standardized volumes (e.g. 10 ml/kg) of administered fluid may not produce equivalent alterations in preload between patients. This is due to variability in (a) baseline blood volume, (b) mechanics of the venous vasculature (capacitance, compliance and resistance), (c) transthoracic pressure gradients, and (d) myocardial diastolic function [14, 15]. Second, patients with diminished contractility will manifest a flatter gradient of the Frank–Starling curve, yielding smaller changes in stroke volume for a given change in preload [16, 17].

Prediction of fluid responsiveness remains relatively underexplored in the paediatric intensive care unit (PICU), perhaps because of the challenges of cardiac output measurement. To date, most studies are small (typically less than 50 patients), and thus potentially both underpowered and prone to type 1 error [5]. None, to our knowledge, have addressed the two haemodynamic factors alluded to above. Thus, we aimed to evaluate volume responsiveness in a large PICU cohort ($n = 100$), using an accurate, indicator dilution method for cardiac output measurement. Our aims were threefold:

1. To evaluate the predictive ability (stroke volume increase greater than 15 % after fluid administration) of a range of static and dynamic variables derived using two commercially available devices.
2. To document typical changes in volumetric variables after a constant fluid bolus (10 ml/kg), and investigate factors associated with change in preload (end-diastolic volume).
3. To investigate whether the baseline myocardial contractile status influences stroke volume response and hence predictive ability.

Methods

This prospective, non-randomized study was conducted within a 20-bed multidisciplinary PICU, after ethics committee approval and parental informed consent. Detailed methodology is available in the electronic supplement. Briefly, haemodynamic measurements were made within 24 h of admission, timed to coincide with fluid bolus administration. Fluid boluses (10 ml/kg of crystalloid over 20 min) were administered at the discretion of the attending clinicians, who were blinded to the advanced haemodynamic measurements. Variables were measured less than 15 min before and up to 30 min after fluid administration.

Standard haemodynamic variables included heart rate, arterial and central venous pressures. Advanced haemodynamic variables (Table 1) were measured using two commercially available devices. The first, CO-Status™ (Transonic systems, Ithaca, NY), uses an indicator dilution method: transpulmonary ultrasound velocity [18]. Cardiac output is calculated via the Stewart–Hamilton equation after venous injection of a small volume of 0.9 % saline; several static volumetric variables are also calculated from the curve properties (Table 1 and online supplement) [10]. The second device, Mostcare® (Vytech®, Padova, Italy) is a continuous system utilizing arterial pulse contour analysis (pressure recording analytical method, PRAM) [19]. This calculates beat-to-beat stroke volume via a custom algorithm, as well as a range of dynamic variables (Table 1). Variability measures (e.g. pulse pressure variability) were averaged over 30 s.

A positive fluid response was described as an increase in stroke volume index (SVI) of at least 15 % after fluid bolus. We chose arterial dp/dt_{MAX} as a measure of systemic ventricular contractility, as this correlates closely with intraventricular dp/dt_{MAX} [20]. Arterial load was as expressed as effective arterial elastance, using the Segers formula [21]. Cardiac volumetric data were allometrically scaled to body surface area using a power of 1.38 [i.e. $(m^2)^{1.38} = m^{2.6}$]; hence volumes are expressed as $ml/m^{2.6}$ [22, 23].

Inclusion criteria were (1) weight ≥2 kg, (2) age ≤16 years, (3) pre-existing arterial and central venous lines. Exclusion criteria were (1) significant valvular regurgitation, (2) large anatomical shunts, (3) residual left-sided obstructive lesions (e.g. aortic stenosis, coarctation), (4) extreme haemodynamic instability, (5) arrhythmias. Exclusions 1–3 were screened using transthoracic echocardiography. Patients with repaired single ventricle physiology (i.e. post Fontan operation) were included, as this should not compromise indicator dilution-based cardiac output assessment. However, the effect on intravascular volume estimation (which relies on mean transit times) is unknown; thus, a sensitivity analysis was anticipated (with and without Fontan patients).

Table 1 Advanced haemodynamic variables measured

Advanced haemodynamic variables	Abbreviation	Units	Modality	Definition
Stroke volume index	SVI	ml/m$^{2.6}$	TPUD	Volume of blood ejected from the heart during a single cardiac cycle
Cardiac index	CI	L/min/m$^{2.6}$	TPUD	Volume of blood ejected from the heart per minute
Systemic vascular resistance index	SVRI	Dyne s/cm^5/m$^{2.6}$	TPUD	Mean arterial−central venous pressure × 80/cardiac index
Effective arterial elastance	EAE	mmHg/ml/m$^{2.6}$	TPUD	Composite measure of arterial load, based on a 2-element Windkessel model that includes peripheral resistance and total arterial compliance
Static variables				
Total end-diastolic volume index	TEDVI	ml/m$^{2.6}$	TPUD	Sum of end-diastolic volumes of the atria and ventricles
Central blood volume index	CBVI	ml/kg	TPUD	Volume of blood between the injection (central vein) and recording (artery) sites, which includes the volume of blood in the heart, lungs, and large vessels
Active circulating volume index	ACVI	ml/kg	TPUD	Volume of blood in which the indicator (saline) mixes in 1 min from the time of injection
Maximum rate of systolic arterial pressure rise	dp/dt_{MAX}	mmHg/s	PRAM	Maximum rate of systolic arterial pressure rise
Dynamic variables				
Systolic pressure variation	SPV	%	PRAM	Difference between the maximum and minimum systolic pressures divided by mean systolic pressure during one mechanical breath
Pulse pressure variation	PPV	%	PRAM	Difference between the maximum and minimum pulse pressures divided by mean pulse pressure during one mechanical breath
Stroke volume variation	SVV	%	PRAM	Difference between the maximum and minimum stroke volume divided by mean stroke volume during one mechanical breath

TPUD transpulmonary ultrasound dilution, *PRAM* pressure recording analytical method

Statistical methods

Data are expressed as mean (±SD) or median (IQR). Bivariate comparisons were via unpaired *t* tests. Models evaluating factors predicting and explaining fluid response were constructed using multilevel logistic and linear regression, respectively (adjusted for multiple measurements within patients). Model fit was quantified by the area under the receiver operating characteristic curve (AUROC) for logistic models, and adjusted r^2 for linear. Collinearity was quantified via the variance inflation factor. The statistical software was Stata v13.1 (StataCorp Texas).

Results

Study population and measurements

One hundred mechanically ventilated children, median (IQR) age 18 (6–48) months and weight 10 (5.6–15) kg, were enrolled between September 2010 and May 2012. The majority were admitted following cardiac surgery (supplement Table E2). Two subsets of this population have been published elsewhere [24, 25], and abstract results containing the first 47 patients are reported in a systematic review [5].

A total of 169 paired (pre- and post-fluid) measurements were taken; no patient had more than four measurement pairs. On review of the raw data from the dilution curves and PRAM outputs, 27 measurements were rejected because of poor signal quality or data capture issues, leaving 142 measurements for final analysis. Of these, 116 (82 %) were taken while patients were receiving inotropic agents (predominantly milrinone), and 19 (13 %) were receiving vasopressors. All patients were mechanically ventilated in SIMV mode (see Table E3). Muscle relaxants were not routinely used; however, sedation level was titrated to minimise spontaneous respirations, as evidenced by concordance of the set SIMV and measured patient respiration rates (Table E3). None received renal replacement therapy. The overall response rate (SVI increase at least 15 %) was 45.1 % (64/142).

Prediction of fluid responsiveness

There were no significant differences in baseline, basic haemodynamic data between responders and non-

Table 2 Baseline haemodynamic variables according to fluid responsiveness

Haemodynamic variable	Units	Response ($n = 64$)	Non-response ($n = 78$)	p	AUROC (95 % CI)
Basic					
Heart rate	bpm	141 (23)	135 (22)	0.10	–
Central venous pressure	mmHg	8.8 (3.7)	9.1 (3.5)	0.66	0.53 (0.43–0.63)
Systolic blood pressure	mmHg	93 (21)	87 (18)	0.07	–
Diastolic blood pressure	mmHg	51 (11)	49 (10)	0.27	–
Advanced: routine					
Stroke volume index	ml/m$^{2.6}$	28 (8)	34 (12)	0.001	–
Cardiac index	L/min/m$^{2.6}$	3.9 (1.1)	4.5 (1.6)	0.01	–
Systemic vascular resistance index	Dyne s/cm^5/m$^{2.6}$	1267 (624)	1067 (456)	0.03	–
Effective arterial elastance	mmHg/ml/m$^{2.6}$	2.59 (1.1)	2.08 (0.89)	0.002	–
Advanced: static					
Total end-diastolic volume index	ml/m$^{2.6}$	259 (75)	306 (82)	<0.001	0.67 (0.58–0.76)
Central blood volume index	ml/kg	16.1 (3.6)	17.7 (5.1)	0.04	0.59 (0.49–0.68)
Active circulating volume index	ml/kg	46.2 (11.8)	53.3 (15.5)	0.003	0.64 (0.55–0.73)
Maximum rate of systolic arterial pressure rise	mmHg/s	1116 (392)	958 (346)	0.01	0.61 (0.52–0.70)
Advanced: dynamic					
Systolic pressure variation	%	12.6 (8.6)	10.4 (6.8)	0.10	0.59 (0.50–0.69)
Pulse pressure variation	%	23.3 (11.2)	21.8 (9.4)	0.38	0.54 (0.44–0.64)
Stroke volume variation	%	22.9 (6.8)	23.3 (7.7)	0.79	0.53 (0.43–0.62)

Data are presented as mean (SD) and refer to paired measurement episodes ($n = 142$)
AUROC area under receiver operating characteristic curve, *bpm* beats per minute

responders (Table 2). However, responders demonstrated lower stroke volumes and cardiac indices and higher systemic vascular resistance and effective arterial elastance.

Responders had significantly different values than non-responders for all baseline static haemodynamic variables, but for none of the dynamic variables (Table 2). Of relevance to the dynamic variables, there were no differences between the two groups in terms of expiratory tidal volumes: 12.0 ± 3.3 versus 11.8 ± 3.8 ml/kg ($p = 0.73$) or respiratory rate 18.4 ± 2.2 versus 18.6 ± 2.2 ($p = 0.69$).

Despite these statistical differences, overall prediction was poor, with static volumetric variables generally performing better than dynamic variables in terms of AUROC (Table 2). The highest predictive value was demonstrated for TEDVI (AUROC 0.67), with optimal prediction occurring at TEDVI of 240 ml/m$^{2.6}$. This yielded sensitivity 45.3 %, specificity 85.9 %, and correct classification rate 67.6 %. Prediction improved significantly when dp/dt_{MAX} was added as a second predictor to TEDVI (AUROC increased from 0.67 to 0.71, $p = 0.02$).

Factors associated with change in preload (total end-diastolic volume)

Fluid bolus increased TEDVI, on average by 34.6 ± 34.2 ml/m$^{2.6}$ for responders and 8.4 ± 34.7 ml/m$^{2.6}$ for non-responders ($p < 0.001$). There were similar inter-group differences for other volumetric variables: delta CBVI (2.2 ± 2.3 versus −0.11 ± 2.4 ml/kg, $p < 0.001$), delta ACVI (6.3 ± 5.4 versus 0.4 ± 5.4 ml/kg, $p < 0.001$). The correlation between delta TEDVI and delta CBVI was $r = 0.71$, $p < 0.001$, which was higher than that for delta TEDVI and delta ACVI, $r = 0.42$, $p < 0.001$. Delta TEDVI did not have a significant correlation with delta central venous pressure, $r = 0.14$, $p = 0.10$, nor delta heart rate, $r = 0.08$, $p = 0.37$. Also, there was no difference in heart rate change after volume between responders and non-responders (mean change −4.7 versus −3.2 beats/min, $p = 0.24$).

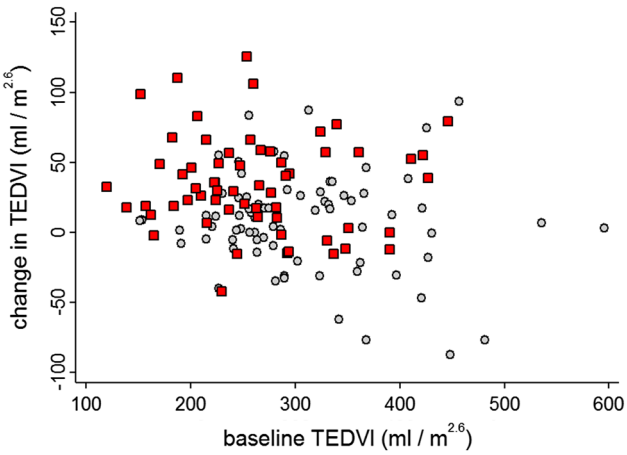

Fig. 1 Scatterplot showing baseline versus change in total end-diastolic volume after fluid administration. *TEDVI* total end-diastolic volume index. *Grey circles* represent patients who did not respond to fluid bolus, *red squares* represent responders

There was a weak inverse relationship between delta TEDVI and baseline TEDVI ($r = -0.19$, $p = 0.02$; Fig. 1), but none between delta TEDVI and baseline

Table 3 Regression model quantifying the relationship between haemodynamic factors and change in stroke volume index after fluid bolus

Haemodynamic factor	Variable	Unit of measurement	Coefficient	95 % CI	*p*	Partial R^2	VIF
Change in preload	ΔTEDVI	per 10 ml/m$^{2.6}$	0.84	0.67–1.01	<0.001	0.40	1.02
Baseline contractility	d*p*/dt_{MAX}	per 100 mmHg/s	0.31	0.14–0.48	<0.001	0.08	1.01
Arterial load	EAE	per mmHg/ml/m$^{2.6}$	0.14	−0.49 to 0.77	0.66	0.001	1.01

The overall model R^2 was 0.45
CI confidence interval, *VIF* variance inflation factor

central venous pressure ($r = -0.03$, $p = 0.72$), expiratory tidal volume ($r = -0.01$, $p = 0.89$), d*p*/dt_{MAX} ($r = 0.10$, $p = 0.24$) or arterial load ($r = -0.02$, $p = 0.83$, see supplement Fig. E2).

Factors influencing fluid responsiveness

We investigated the joint influence of change in preload (delta TEDVI), baseline systemic ventricular contractility, and arterial load on the change in stroke volume (delta SVI) after fluid bolus using multivariable linear regression (Table 3; Fig. 2). The model explained 45 % of the variability in delta SVI after fluid bolus, with delta TEDVI being the dominant factor, exhibiting a partial R^2 value approximately five times greater than that for contractility (d*p*/dt_{MAX}). Of note, arterial load was not related to delta SVI.

Although delta TEDVI explained the majority of the variability in delta SVI, baseline contractility was nonetheless an important factor. This is shown in Fig. 3, which was constructed using the regression coefficients from Table 3. Here the grey horizontal bar represents the cut-off whereby a positive delta SVI response is defined as at least 15 %. Children with high baseline contractility, defined as a d*p*/dt_{MAX} ≥75th centile (≥1300 mmHg/s), typically achieved a positive SVI response with delta TEDVI values of 10–15 ml/m$^{2.6}$, whereas patients with low contractility (d*p*/dt_{MAX} ≤25th centile, ≤800 mmHg/s), typically required delta TEDVI values of 35–40 ml/m$^{2.6}$.

Sensitivity analysis

Analyses were repeated ($n = 114$) after excluding single ventricle patients (post Fontan procedure). This produced a significant improvement in predictive ability for d*p*/dt_{MAX}, with AUROC increasing from 0.61 to 0.68 (see supplement Table E4). For other variables, the predictive ability changed only slightly and not consistently. For example, the AUROC increased for TEDVI (from 0.67 to 0.69), but decreased for PPV (from 0.54 to 0.51). In terms of "factors associated with change in preload" (see above), exclusion of Fontan patients did not produce

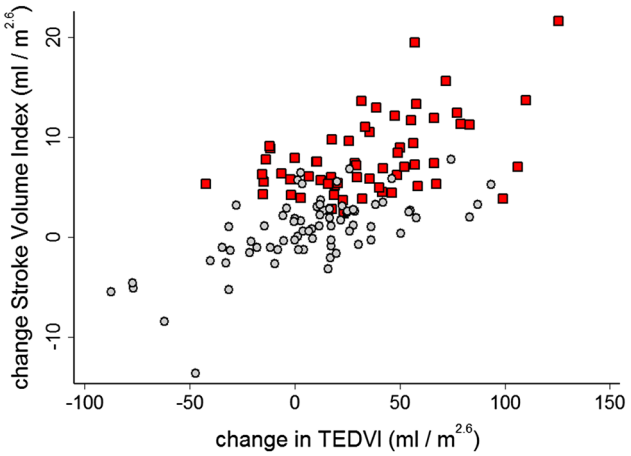

Fig. 2 Scatter plot demonstrating the relationship between absolute change in stroke volume index and absolute change in total end-diastolic volume index after fluid administration. *TEDVI* total end-diastolic volume index. *Grey circles* represent patients who did not respond to fluid bolus, *red squares* represent responders

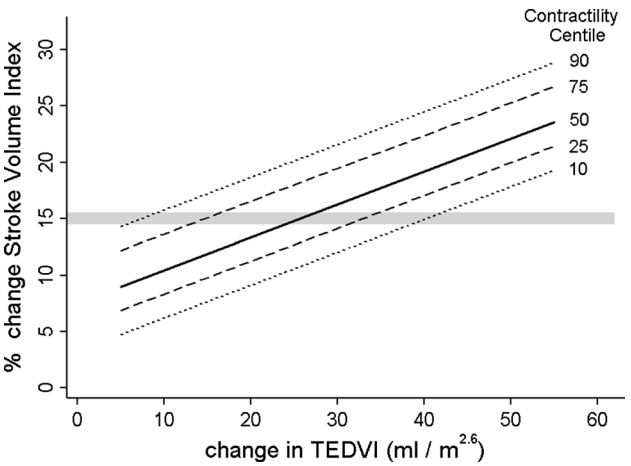

Fig. 3 Regression-derived multivariable relationship between percentage change in stroke volume index and absolute change in total end-diastolic volume index after fluid administration, taking into account baseline contractile state. *TEDVI* total end-diastolic volume index. *Isobars* represent centiles of contractility (d*p*/dt_{MAX}) for the study population. The *grey horizontal bar* represents the cut-off when a positive delta stroke volume index response is defined as at least 15 %

major qualitative changes in the relationship between delta TEDVI and any variable. For "factors influencing fluid responsiveness", Fontan exclusion improved regression model fit (R^2 increased from 0.45 to 0.53); however, the coefficients and p values for individual variables changed little.

Discussion

Our first aim was to evaluate potential predictors of volume response using two novel, commercially available devices. Overall the predictive ability of most variables was poor, with static variables performing better than dynamic (see Table 2). This is largely concordant with Gan's systematic review (12 studies, 438 children), which demonstrated limited predictive ability across a broader range of static and dynamic variables using different measuring devices to those in our study [5]. Our AUROC values compared to Gan[1] are as follows: central venous pressure 0.53 versus 0.54, cardiac end-diastolic volumetric variables 0.67 versus 0.62, systolic pressure variability 0.59 versus 0.63, pulse pressure variability 0.54 versus 0.71, stroke volume variability 0.53 versus 0.69. The larger between-study AUROC differences for the last two variables have possible explanations. For pulse pressure variability, Gan's higher AUROC is influenced by one outlier study; when this is excluded the value falls to 0.61 [5]. For stroke volume variability, our lower AUROC may be due to different methods of calculation. We used PRAM, which was not assessed by Gan; this technology may provide an inaccurate estimate of paediatric stoke volume [24], and predicts volume response poorly in adult studies, yielding an AUROC of 0.60 [26].

It is interesting to note that the predictive ability for the dynamic, arterial waveform-derived variables is markedly lower in children compared to adults, where typical AUROC values range from 0.84 to 0.96 [27, 28]. This may be due to age-related differences in vascular mechanical properties, affecting arterial waveform behaviour. There are dramatic (at least twofold) changes in both total arterial compliance and aortic characteristic impedance (normalized to body surface area) from birth to adulthood [29, 30], associated with changes in arterial vessel wall thickness and collagen fibre quantity/length [31]. There are also inherent differences in vascular properties within paediatric pathologies. For example, in congenital cardiovascular disease, average arterial elastance may exhibit twofold differences, dependent upon the anatomic cardiac lesion, being both higher and lower than that for normal children [32].

[Par28]Calculated using pooled, weighted data from relevant studies within Gan [5].

However, arterial mechanical factors would likely only explain a proportion of the differences between paediatric and adult studies. Thus, our second and third aims involved investigating factors that may affect predictive ability. Unsurprisingly, the largest determinant of change in SVI with volume loading was change in preload, as measured by TEDVI. However, preload did not change in a consistent fashion after volume loading, with delta TEDVI being only weakly correlated with baseline TEDVI (Fig. 1). This relationship was three to four times weaker in our patients compared to adults with sepsis [33], and in an animal haemorrhagic model [34], yielding correlation coefficients of −0.19 (current study), versus −0.65 and −0.73, respectively. We do not know the reason for this, but speculate that it may be due to variable degrees of systemic inflammation and capillary leak, differences in diastolic function [35, 36] and venous mechanics [37, 38] in paediatrics. Of note, very little is known about the mechanics of venous return in paediatric critical illness [39].

Our third finding emphasized the importance of considering systemic ventricular contractility when assessing predictive ability of end-diastolic volume. Although highlighted by others, this has only been quantified in terms of change in AUROC when contractility is dichotomized as "poor" versus "preserved" [40, 41]. We have extended these findings, by considering contractility as a continuous variable (Table 3; Fig. 3), allowing for a more precise quantification. This shows that a patient with poor baseline contractility needs an absolute increase in end-diastolic volume approximately 3–4 times greater than a patient with good contractility (i.e. 35–40 versus 10–15 ml/m$^{2.6}$) to achieve SVI "responder" status (i.e. SVI increment of at least 15 %). This obviously requires higher volumes of fluid loading: Reuter showed that critically ill adult patients with reduced contractility require on average 25 ml/kg of 6 % hetastarch to reach the top of their Starling curves [17]. The clinical implications are important for patients with reduced contractility, who will require increased volume administration if a stroke volume increase of greater than 15 % is targeted, but are also at higher risk of inadequate fluid clearance and hence fluid overload [42]. Earlier inotrope usage with judicious fluid administration may be a preferable strategy for such patients.

Study limitations

1. SVI and the volumetric variables (TEDVI, ACVI and CBVI) were derived from aspects of the ultrasound dilution curve, raising the possibility of mathematical coupling. Reassuringly, however, several clinical and animal studies have shown that coupling is unlikely with transpulmonary dilution curves, as volumetric variables remained constant when stroke volume was altered with beta agonists/blockers [33, 43, 44].

2. We may not have evaluated stoke volume variability accurately, as PRAM has been found to be an inaccurate measure of SVI [24]. This may explain the discrepancy between our findings and the good prediction (AUROC 0.85) for aortic peak velocity, a variable closely related to stroke volume variability [45]. However, there is no reason to believe a similar error is present with PPV or SPV, as these were calculated directly from the arterial line.
3. Spontaneous ventilation can compromise the predictive value of dynamic variables. Although our patients were ventilated in SIMV mode, the concordance of the set SIMV and measured patient respiration rates (Table E3) suggests that very little spontaneous respiration was occurring. Also, our AUROC for the dynamic variables were similar to other paediatric studies using CMV (see the first paragraph of "Discussion").
4. We used only one indirect measure of contractility (dp/dt_{MAX}) derived from the arterial rather than the left ventricular waveform. However, this correlates closely with invasively measured intraventricular dp/dt_{MAX} in children [20]. Also, the PRAM estimate of dp/dt_{MAX} appears valid (despite being inaccurate for SVI) when compared to echocardiographically derived dp/dt_{MAX} in adults [46]. It also tracks changes in inotropic state accurately in adults [47]. A limitation of this measure is its sensitivity to changes in preload [47]. However, this potential collinearity did not appear to be significant in our study, given the low regression variance inflation factors (Table 3).
5. We did not assess the influence of venous mechanics on TEDVI response to volume loading. Bedside techniques for this are still relatively novel in adult practice [48], and pose distinct challenges in terms of paediatric application.
6. Clinical indications for fluid administration were not recorded. The likelihood of volume response may possibly differ according to clinical indication or perhaps clinician seniority. Interestingly, a recent multicentre study has highlighted enormous variability with fluid challenges, in terms of indication, type, volume and assessment of response [49].

We suggest that these limitations are unlikely to change the three fundamental findings of our study. First, haemodynamic variables predict response to volume poorly when SVI response is dichotomized as less than or at least 15 %. Second, volume loading does not produce consistent changes in ventricular end-diastolic volumes. Third, baseline contractility plays an important role in influencing volume response. Paediatric studies investigating the role of venous mechanics in volume response are needed. We also suggest that more information would be gained from future studies if SVI response is expressed as a continuous variable.

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Compliance with ethical standards

Conflicts of interest No conflicts of interest are declared for any author.

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