Cardiac Preload Responsiveness in Children With Cardiovascular Dysfunction or Dilated Cardiomyopathy: A Multicenter Observational Study*

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Objectives: To characterize cardiac preload responsiveness in pediatric patients with cardiovascular dysfunction and dilated cardiomyopathy using global end-diastolic volume index, stroke volume index, cardiac index, and extravascular lung water index.

Design: Prospective multicenter observational study.

Setting: Medical/surgical PICUs of seven Spanish University Medical Centers.

Patients: Seventy-five pediatric patients (42 male, 33 female), median age 36 months (range, 1–207 mo), were divided into three groups: normal cardiovascular status, cardiovascular dysfunction, and dilated cardiomyopathy.

Interventions: All patients received hemodynamic monitoring with $PiCCO_2$ (Pulsion Medical System SE, Munich, Germany). We evaluated 598 transpulmonary thermodilution sets of measurements. In 40 patients, stroke volume index, cardiac index, and global end-diastolic volume index were measured before and after 66 fluid challenges and loadings to test fluid responsiveness at different preload levels.

Measurements and Main Results: Global end-diastolic volume versus predicted body surface area exhibits a power-law relationship: Global end-diastolic volume = 488.8·predicted body surface area$^{1.388}$ ($r^2 = 0.93$). Four levels of cardiac preload were established from the resulting "normal" global end-diastolic volume index (= 488.8·predicted body surface area$^{0.388}$). Stroke volume index and cardiac index versus global end-diastolic volume index/normal global end-diastolic volume index built using a linear mixed model analysis emulated Frank-Starling curves: in cardiovascular dysfunction group, stroke volume index (geometric mean [95% CI]) was 27 mL/m^2 (24–31 mL/m^2) at "≤ 0.67 times normal global end-diastolic volume index," 37 mL/m^2 (35–40 mL/m^2) at "> 0.67 ≤ 1.33 times normal global end-diastolic volume index" (Δ stroke volume index = 35%; $p < 0.0001$; area under the receiver-operating characteristic curve = 75%), 45 mL/ m^2 (41–49 mL/m^2) at "> 1.33 ≤ 1.51 times normal global end-diastolic volume index" (Δ stroke volume index = 21%; $p < 0.0001$; area under the receiver-operating characteristic curve = 73%), and 47 mL/m^2 (43–51 mL/m^2) at "> 1.51 times normal global end-diastolic volume index" (Δ stroke volume index = 4%; $p = 1$; area under the receiver-operating characteristic curve = 54%). In dilated cardiomyopathy group, stroke volume index was 21 mL/m^2 (17–26 mL/m^2) at "> 0.67 ≤ 1.33 times normal global end-diastolic volume index," 27 mL/m^2 (21–34 mL/ m^2) at "> 1.33 ≤ 1.51 times normal global end-diastolic volume index" (Δ stroke volume index = 29%; $p = 0.005$; area under the receiver-operating characteristic curve = 64%), and 25 mL/m^2 (20–32 mL/m^2) at "> 1.51 times normal global end-diastolic volume index" (Δ stroke volume index = –8%; $p = 1$; area under the receiver-operating characteristic curve = 54%).

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Dr. de la Oliva received provision of equipment from Pulsion (PiCCO2 monitor, PiCCO catheters), received support from Pulsion (1000 Eur to Secretary for filling out the MS Access database), and received support for travel from Maquet Critical Care (Madrid-Boston flight ticket for manuscript preparation). His institution received grant support from Maquet Critical Care (NAVA software and modules). Dr. Jaraba is employed by the Hospital Reina Sofía Córdoba, Spain. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/PCC.0000000000000286

Conclusions: This study provides "normal" values for global end-diastolic volume index and limits of cardiac preload responsiveness in pediatric patients with cardiovascular dysfunction and dilated cardiomyopathy: 1.33 times normal global end-diastolic volume index represents the upper limit of patent cardiac preload responsiveness, with the highest expected responsiveness being below 0.67 times normal global end-diastolic volume index. The maximum response of the Frank-Starling relationship and therefore the level of no additional preload reserve is 1.33 to 1.51 times normal global end-diastolic volume index. Above 1.51 times normal global end-diastolic volume index preload responsiveness is unlikely, and the risk of pulmonary edema is maximal. (*Pediatr Crit Care Med* 2015; 16:45–53)

Key Words: extravascular lung water; fluid responsiveness; global end-diastolic volume; hemodynamic monitoring; preload responsiveness; shock

Hypovolemia is the major cause of cardiovascular dysfunction in critically ill patients (1). Maintenance of adequate cardiac preload and cardiac output (CO) remains the primary targets to optimize hemodynamics for these patients. Nevertheless, increasing stroke volume (SV) does not necessarily follow after volume expansion as clinical examination is of minimal value for detecting inadequate cardiac preload (2), and the relationship between ventricular preload and SV is curvilinear, as described by Frank-Starling (3). Additionally, overly aggressive volume expansion may produce fluid overload leading to pulmonary edema and worsening gas exchange.

Fluid responsiveness is defined as a clinically meaningful increase in SV, generally greater than 15%, following a fluid challenge (4). According to the Frank-Starling curvilinear relationship, a patient is a "responder" to volume expansion only if both ventricles are preload responsive, which occurs when they are working in the steep part of the curve (3).

For predicting fluid responsiveness, it has been recommended that it should be determined on the part of the Frank-Starling relationship that the heart is actually working (5). Global end-diastolic volume (GEDV) is determined by transpulmonary thermodilution (TPTD) and measures the volume of blood in the four chambers of the heart, making it a good variable for evaluating cardiac preload in adults and children (6–9). Therefore, GEDV versus SV and/or CO may be used to establish the Frank-Starling relationship. Nevertheless, more information is currently needed to establish cutoff values of global end-diastolic volume index (GEDVI) for predicting cardiac preload responsiveness especially in children in whom the "normal" GEDVI values have not been established.

Pulmonary edema is a harmful consequence of fluid overload. Extravascular lung water (EVLW) determined at the bedside using TPTD has been shown to be a sensitive prognostic indicator of pulmonary edema (10), and its increase has recently been found to be associated with the Frank-Starling plateau (6).

We hypothesized that the limits for cardiac preload responsiveness could be ascertained using the combination of GEDV,

TABLE 1. Characteristics of Pediatric Intensive Care Patients

Patient Group	Patients	Age (mo)		Gender		PICU Stay, Days, Median (IQR)	TPTD Assessments
		Median (IQR)	Range	Male	Female		
Normal cardiovascular status	27	48 (19–121)	2–201	12	15	12 (6–24)	53
Cardiovascular dysfunction	61	36 (12–104)	1–207	34	27	19 (11–34)	420
Dilated cardiomyopathy	10	20 (4–93)	2–146	5	5	14 (10–37)	73
Total	75	36 (12–104)	1–207	42	33	12 (7–28)	532

IQR = interquartile range (25–75%), TPTD = transpulmonary thermodilution, ARF = acute respiratory failure, ND = near-drawing.
A total of 23 patients had TPTD assessments in both the normal cardiovascular function and cardiovascular dysfunction groups. In the cardiovascular dysfunction group, one patient with hepatic transplantation stayed for 198 days in the PICU.

SV (CO), and EVLW. The aim of the current study was to characterize the relationships of GEDV-based cardiac preload with SV (CO) and EVLW in pediatric patients with acute cardiovascular dysfunction and dilated cardiomyopathy.

PATIENTS AND METHODS

This was a prospective multicenter observational study (ClinicalTrials.gov identifier NCT01157299) including pediatric patients consecutively admitted to the PICUs of seven Spanish University Hospitals from July 2009 to February 2011. Written informed consent was obtained from parents. The study was approved by the Ethics Committee from each center.

Pediatric patients admitted to the PICU and equipped with a femoral arterial catheter and a central venous catheter (internal jugular or femoral) or who required advanced hemodynamic monitoring were consecutively enrolled to receive TPTD assessments of SV, CO, GEDV, and EVLW with the $PiCCO_2$ monitor (Pulsion Medical System SE, Munich, Germany). Patients with left to right cardiac shunts on extracorporeal membrane oxygenation or less than 4 kg body weight were excluded.

$PiCCO_2$ hemodynamic variables were indexed to body surface area (BSA), predicted BSA (PBSA), or predicted body weight (PBW) according to Pulsion Medical System SE recommendations: stroke volume index (SVI) = SV/BSA, cardiac index (CI) = CO/BSA, GEDVI = GEDV/PBSA, and extravascular lung water index (EVLWI) = EVLW/PBW.

In order to test the patient's fluid responsiveness, SVI, CI, and GEDVI were measured before and after those volume loadings and fluid challenges indicated by the physician in charge of the patient admitted to the study and already connected to the $PiCCO_2$ monitor. Fluid responsiveness was defined as an increase in SVI or CI of at least 15% (4).

Patients were classified according to their hemodynamic status at the moment of the TPTD assessments of GEDVI, SVI, CI, and EVLWI into normal cardiovascular status, cardiovascular dysfunction, or dilated cardiomyopathy.

Normal cardiovascular status was established if at the moment of the TPTD assessment the patient showed no clinical evidence of end-organ hypoperfusion, systolic blood pressure (SBP) greater than 5th percentile for age, normohydration, not on high-frequency oscillatory ventilation, no evidence of systemic inflammatory response syndrome (SIRS)/sepsis, CI 3.3–6 L/min/m^2, serum lactate less than or equal to 2 mmoL/L, $ScvO_2$ greater than or equal to 70%, and vasoactive inotropic score (VIS) (11) of 0 μg/kg/min.

Cardiovascular dysfunction was established if at the moment of the TPTD assessment the patient fulfilled the following criteria modified from the International Pediatric Sepsis Consensus Conference (12): SBP or mean blood pressure (MBP) less than 5th percentile for age or need for vasoactive or inotropic drugs (VIS ≥ 5 μg/kg/min) to maintain MBP greater than 5th percentile for age or two of the following: unexplained metabolic acidosis (base deficit < 5.0 mEq/L), increased arterial lactate greater than two times upper limit of normal, oliguria (urine output < 0.5 mL/kg/hr), capillary refill greater than 5 seconds, core to peripheral temperature gap greater than 3°C, $ScvO_2$ less than 70% or oxygen extraction fraction (O_2ER =

Mechanical Ventilation		
On TPTD Assessments	Positive End-Expiratory Pressure, cm H_2O, Median (IQR)	Disease at PICU Admission
29 (54.7%)	5 (5–7)	ARF (1), cranial trauma (1), hypertensive emergency (1), ND (1)
320 (76.1%)	6 (5–8)	ARF (7), bronchopneumonia (3), burn (3), digestive hemorrhage and hemoperitoneum (1), hepatic failure and sepsis (3), hemophagocytic syndrome and sepsis (2), hepatic transplantation (1), influenza A H1N1 and congenital immunodeficiency (1), intracerebral hemorrhage (3), Kawasaki disease (1), Lyme disease (1), meningococcal sepsis (7), ND (1), neurogenic pulmonary edema secondary to a posterior fossa tumor (1), postobstructive pulmonary edema secondary to laryngospasm (1), postoperative sepsis (5), pulmonary transplantation (1), polytrauma (1), respiratory syncytial virus bronchiolitis (5), sepsis and congenital immunodeficiency (2), status epilepticus and shock (4), sepsis in oncology patient (6), sepsis associated to retropharyngeal abscess due to *Fusobacterium necrophorum* (1)
39 (53.4%)	6 (5–7)	Dilated cardiomyopathy
388 (71.0%)	6 (5–8)	

(Sao_2 – $Scvo_2$)/Sao_2) greater than 30%, CI less than 3.3 L/min/m^2 in a SIRS/septic patient or CI less than 3 L/min/m^2 in non-SIRS/septic patient, and maintained CI greater than 6 L/min/m^2 in a SIRS/septic patient.

Dilated cardiomyopathy was defined as dilated, hypocontractile left ventricle on echocardiogram (ejection fraction < 50%) with absence of the following identifiable causes of ventricular dysfunction: congenital heart disease, cardiotoxic agents, Kawasaki disease, chronic primary arrhythmias, bacterial sepsis, postischemic injury, or HIV infection.

Data from patients who did not fulfill any of these criteria at the moment of TPTD assessment or with congenital heart disease or heart transplantation were recorded but excluded from this study. Data from the normal cardiovascular status group were used to establish the normal GEDVI values ($GEDVI_N$) and their limits in children. The remaining data, excluding postvolume loading observations, were used to characterize the relationships of GEDVI-based cardiac preload with SVI (CI) and EVLWI.

Statistical Analysis

Linear and nonlinear analyses were used to examine the PBSA-GEDV relationship in patients with normal cardiovascular status. The model with the highest R^2 value, the lowest residual mean square, and the lowest square root of residual mean was considered to provide "best fit." On the basis of preliminary exploratory analysis, a power function was used to establish the predicted "normal" GEDVI values ($GEDVI_N = a \cdot PBSA^b$) and limits. GEDVI was normalized accordingly as $GEDVI/GEDVI_N$.

Data were checked for normality of distribution and equality of variance, and a log transformation was applied to dependent variables. To determine the effects of the preload status on CI, SVI, and EVLWI, we used a linear mixed model analysis with restricted maximum likelihood estimation. We modeled the subject identity as the independent random factor with

TABLE 2. Differences of the Hemodynamic Variables Among Groups

	Global End-Diastolic Volume Index/ Normal Global-End Diastolic Volume Index	Stroke Volume Index (mL/m^2)	Cardiac Index (L/min/m^2)	Extravascular Lung Water Index (mL/kg)	Mean Blood Pressure (mm Hg)	$Scvo_2$ (%)	Oxygen Extraction Rate (%)	Vasoactive Inotropic Score (μg/kg/min)
Normal cardiovascular status								
Geometric mean	1.01	41	4.7	15	80	78	18	No catecholamines
95% CI	0.96–1.07	37–44	4.4–5.1	13–17	75–85	74–82	16–21	
Minimum-maximum	0.66–1.49	23–67	3.2–6	7–29	59–128	70–92	8–29	
Cardiovascular dysfunction								
Geometric mean	1.13	40	4.6	16	70	74	20	18.6
95% CI	1.10–1.17	37–42	4.3–4.8	15–18	67–72	71–77	19–22	15.3–22.7
Minimum-maximum	0.49–3.23	14–80	1.6–9.5	4–86	22–116	30–97	3–69	0–181
Dilated cardiomyopathy								
Geometric mean	1.16	22	2.8	22	61	67	29	11.1
95% CI	1.10–1.23	19–44	2.5–3.3	16–28	56–67	62–74	23–37	7.0–17.5
Minimum-maximum	0.72–2.23	11–53	1.3–5.1	8–59	38–86	35–84	16–65	0–45
Normal CVS vs CV dysfunction								
p	0.014	1	0.80	0.13	< 0.0001	0.023	0.31	
AUC (%)	60	52	54	54	68	58	55	
Normal CVS vs dilated cardiomyopathy								
p	0.002	< 0.0001	< 0.0001	0.04	< 0.0001	0.015	0.0017	
AUC (%)	66	72	75	57	74	61	65	
Dilated cardiomyopathy vs CV dysfunction								
p	0.297	< 0.0001	< 0.0001	0.18	0.017	0.19	0.0098	0.041
AUC (%)	54	65	67	53	59	55	58	54

CVS = cardiovascular status, CV = cardiovascular, AUC = area under the receiver-operating characteristic curve.

an unstructured covariance type, the $\log_{10}$ CI, $\log_{10}$ SVI, $\log_{10}$ EVLWI, $\log_{10}$ MBP, $\log_{10}$ $ScvO_2$, $\log_{10}$ O_2ER, and $\log_{10}$ VIS score as the dependent variables, and the GEDVI/$GEDVI_N$ intervals as the fixed independent variable. The post hoc analysis for multiple comparisons between the different preload status intervals was computed with a Bonferroni correction applied. We used the Wilcoxon singed-rank test for comparing the pre and post fluid loading changes in GEDVI and SVI.

As a measure of effect size, we calculated for each pair of data the Cohen *d* using the *t* values from the linear mixed model (13) and the Pearson correlation coefficient *r* computed from Wilcoxon *z* values (14). In order to help to interpret the impact of cardiac preload status change on SVI, CI, and EVLWI, we converted Pearson correlation coefficient *r* and Cohen *d* to the area under the receiver-operating characteristic curve (AUC) = $\Phi(d/\sqrt{2})$, where $d/\sqrt{2}$ is the *z* value and Φ is the cumulative standard normal distribution function (15, 16). AUC represents the probability that a randomly selected subject with a defined cardiac preload status (GEDVI/$GEDVI_N$) will exhibit a different hemodynamic response (higher SVI, CI, or EVLWI) than a randomly selected subject with a lower preload status; minimum AUC = 0.5.

All *p* values less than 0.05 were considered significant. Statistics were computed using SAS 9.2 (SAS Institute, Cary, NC) for Windows.

RESULTS

A total of 890 different TPTD assessments performed in 99 pediatric patients equipped with a femoral arterial and a central venous catheter were recorded. From the 99 patients, only 75 (598 TPTD assessments) who fulfilled the criteria for normal cardiovascular status, cardiovascular dysfunction, or dilated cardiomyopathy were included into the analysis. **Table 1** shows the characteristics of the patients and **Table 2** the hemodynamic variables of every group. Of the 61 patients with cardiovascular dysfunction, 22 had sepsis at admission and 59 fulfilled the criteria for septic shock or had shock associated with SIRS (12) during at least one TPTD assessment throughout their PICU admission, two had burn shock, and one had shock associated with Kawasaki disease. In order to test the patient's fluid responsiveness at distinct preload levels, SVI, CI, and GEDVI were measured in 33 patients with cardiovascular dysfunction and in seven with dilated cardiomyopathy, respectively, before and after 53 (normal saline [NS] 14, albumin 5% [Ab5%] 4, fresh frozen plasma [FFP] 10, packed RBCs [PRBCs] 14, platelets 8, other colloids 3) and 13 (NS 1, hypertonic saline 3% [HS3%] 4, Ab5% 4, PRBCs 4) fluid challenge and fluid loading events. Clinical decisions concerning fluid challenge and fluid loading were made by the PICU physician in charge according to the patient's clinical needs. The median infusion time for the fluid loading and fluid challenge was 33 minutes (interquartile range [IQR], 16–90 min) in the cardiovascular dysfunction and 30 minutes (IQR, 20–30 min) in the dilated cardiomyopathy group. **Figure 1** shows the total volume infused at every preload level in the two groups of patients.

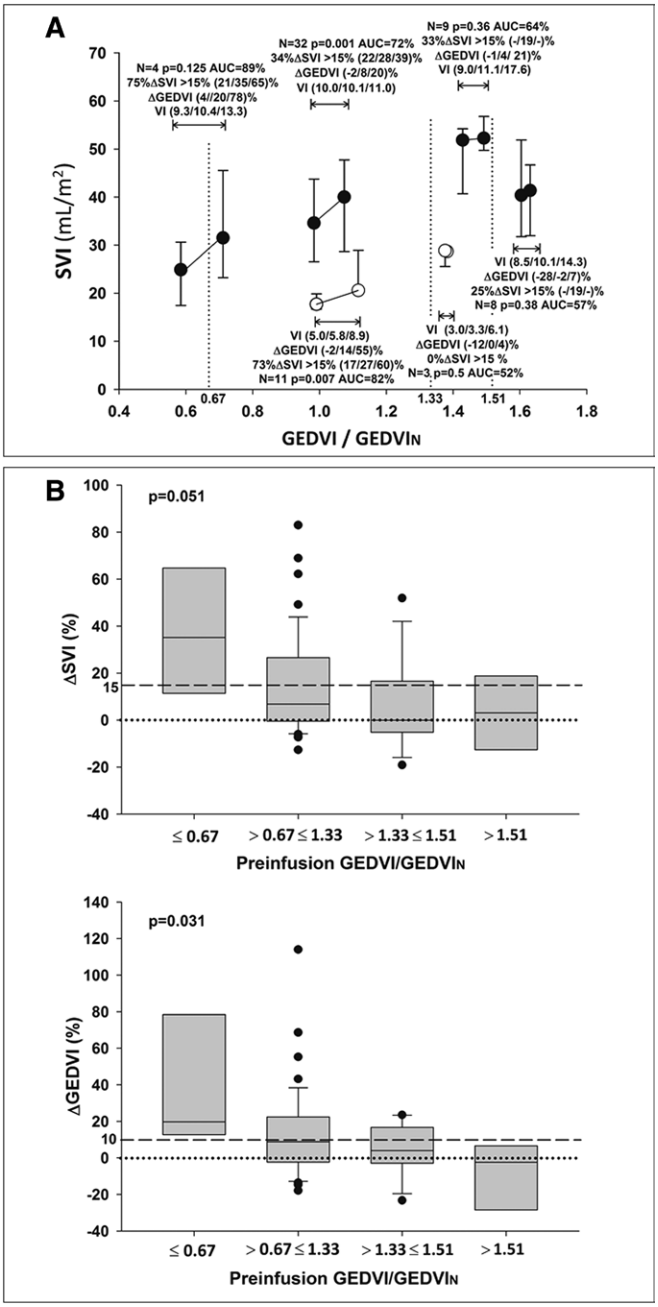

Figure 1. Fluid responsiveness observations. **A**, Stroke volume index (SVI) versus global end-diastolic volume index (GEDVI)/normal global end-diastolic volume index ($GEDVI_N$) before and after fluid loading and fluid challenge in patients with cardiovascular dysfunction (*black circles*) and dilated cardiomyopathy (*white circles*). **B**, Boxplot graphs show the percent of SVI and GEDVI change after volume loading according to patients' preinfusion GEDVI/$GEDVI_N$. The boundary of the box closest to zero indicates the 25th percentile, a *line within the box* marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles. The *black little circles* are the outlying points. Area under the receiver-operating characteristic curve (AUC) represents the probability that a subject with a defined preinfusion cardiac preload status will exhibit a higher SVI after a volume loading and fluid challenge: minimum AUC = 0.5. GEDVI/$GEDVI_N$ = normalized GEDVI, *N* = number of patients (number of fluid loading and fluid challenge), VI = volume infused in mL/kg, ΔGEDVI = % GEDVI change after volume loading and fluid challenge, ΔSVI = % SVI change after volume loading and fluid challenge, ΔSVI > 15% = % patients with a SVI increase > 15% after fluid loading and fluid challenge. Data (in A) are (25th percentile, median, 75th percentile).

GEDV versus PBSA exhibited a power-law relationship: GEDV = 488.8·PBSA$^{1.388}$ (SD = 97.4 mL; R^2 = 0.93; $p < 0.0001$; mean square residual = 0.46). Therefore, "normal" GEDVI (GEDVI$_N$) = 488.8·PBSA$^{0.388}$. The limits of the four levels of cardiac preload, ≤ 0.67, > 0.67 ≤ 1.33, > 1.33 ≤ 1.51, and > 1.51 times GEDVI$_N$ (**Fig. 2**), were set according to 90% and upper 99% GEDVI$_N$ CIs, respectively, and were associated with distinct degrees of cardiac preload responsiveness (**Figs.** 1 and **3**): presence of preload responsiveness below 1.33 times GEDVI$_N$, with the highest expected preload responsiveness below 0.67 times GEDVI$_N$; decreased preload responsiveness above 1.33 times GEDVI$_N$, with the maximum efficacy of the Frank-Starling response between > 1.33 and ≤ 1.51 times GEDVI$_N$; and absence of preload responsiveness with maximum expected lung edema above 1.51 times GEDVI$_N$.

The relationships of GEDVI/GEDVI$_N$ with SVI, CI, and EVLWI are shown in Figure 3. The SVI responses to fluid infusion at the different levels of preinfusion GEDVI/GEDVI$_N$ are presented in Figure 1.

There were no statistically significant differences on SBP between the cardiac preload levels (p = 1): "≤ 0.67 times GEDVI$_N$" 94 (85–104) mm Hg (geometric mean [95% CI]), "> 0.67 ≤ 1.33 times GEDVI$_N$" 98 (95–102) mm Hg, "> 1.33 ≤ 1.51 times GEDVI$_N$" 96 (90–102) mm Hg, and "> 1.51 times GEDVI$_N$" 97 (92–102) mm Hg.

DISCUSSION

In this study, we have established "normal" GEDVI values in children and defined normalized GEDVI limits of cardiac preload responsiveness in children with acute cardiovascular dysfunction and dilated cardiomyopathy.

Fluid loading is the center of treatment in hypovolemia; however, only about 50% of patients respond with a significant increase in CO after fluid loading (17). Additionally, predicting cardiac preload responsiveness is critical because inappropriate fluid administration can result in pulmonary edema and in positive fluid balance, which is associated with increased mortality (18, 19).

Clinical evaluation (20) and measurements of cardiovascular pressures or volumes do not reliably predict fluid responsiveness (17). Although several studies have demonstrated that pressure pulse variation and stroke volume variation are highly predictive of fluid responsiveness, they are of limited use in children as they can only be applied to patients under controlled positive pressure ventilation failing to predict fluid responsiveness in the presence of spontaneous breathing activity (21), low tidal volume (22), low respiratory system compliance (23), high oscillatory frequency ventilation or respiratory rates greater than 40 breaths/min (24), arrhythmias (25), and during increased intra-abdominal pressure (26).

For predicting fluid responsiveness, it has been recommended that it should be determined on the part of the Frank-Starling relationship that the heart is working (5). GEDV behaves as a reliable indicator of preload both in children and adults in different clinical conditions (8, 27). However, there are no "normal" GEDVI values in children, and the proposed normal values in adults (680–800 mL/m^2) are based on measurements in healthy volunteers and are neither appropriate for children (28) nor directly applicable for critically ill patients (29). Since during growth cardiac end-diastolic blood volume increases by a factor of 3, whereas BSA by a factor of 5 (28), a further normalization of GEDVI is required for children. We found that the GEDV-PBSA relationship closely fits a power-law in patients with normal cardiovascular status during the TPTD assessment. Interestingly, both GEDV and left ventricular end-diastolic volume (LVEDV) (30) exhibit a similar power-law relationship with body size, as supported by the similarities of their particular scaling exponents. Assuming a proportional relationship between LVEDV and total cardiac volume, the power-law relationships strongly suggest that the GEDV's increase with body size parallels cardiac volume increase, providing support to the relationship GEDV = 488.8·PBSA$^{1.388}$ for obtaining "normal" values of GEDVI (GEDVI$_N$ = 488.8·PBSA$^{0.388}$) and normalized levels of cardiac preload in children (GEDVI/GEDVI$_N$).

GEDVI/GEDVI$_N$ versus SVI (CI) curves emulate the Frank-Starling biventricular relationship in two groups of patients with distinct contractile states (Fig. 3). These curves depict the probability (AUC) that a subject with a defined cardiac preload status will exhibit a different SVI or CI after a step change in their preload status. Therefore, according to our results, the magnitude of ΔSVI (ΔCI) and the probability for a subject to have a clinically meaningful increase in SVI (CI) after the GEDVI's increase will decrease when his initial preload status is greater than 1.33 times GEDVI$_N$ (starting of the plateau phase), being almost nonexistent above 1.51 times GEDVI$_N$.

These findings are supported by Renner et al (31) who found that GEDVI was a good predictor (AUC, 0.77; sensitivity, 66%; and specificity, 78%) of volume responsiveness (ΔSVI ≥ 15%) after repair of congenital heart disease in 26 anesthetized infants (BSA = 0.46 m^2). Receiver-operating characteristic curve analysis yielded a threshold value of GEDVI less than or equal to 400 mL/m^2 equivalent to 1.11 times GEDVI$_N$. Additionally, Michard et al (8) studied adult patients response to volume in three preinfusion GEDVI groups—low 413–611 mL/m^2, intermediate 615–781 mL/m^2, and high 816–1,174 mL/m^2—and found an increase in the rate of a positive response to volume loading (ΔSVI > 15%) of 77%, 45%, and 23%, respectively. Interestingly, these GEDVI limits correspond with those of our study at 1.80 m^2 PBSA with 816 mL/m^2 matching 1.33 times GEDVI$_N$. In addition, the rate of a positive response was 0% at a preinfusion GEDVI of 950 mL/m^2, equivalent to 1.55 times GEDVI$_N$.

Furthermore, although the number of available fluid loading observations may be insufficient to draw definitive conclusions, data presented in Figure 1 show evidence of patent fluid responsiveness below 1.33 times GEDVI$_N$ in both the cardiovascular dysfunction and dilated cardiomyopathy groups. In fact, the lower the preinfusion preload status, the higher were ΔSVI, ΔGEDVI/GEDVI$_N$, and AUC. By contrast, above 1.33 times GEDVI$_N$, the response to volume loading was less

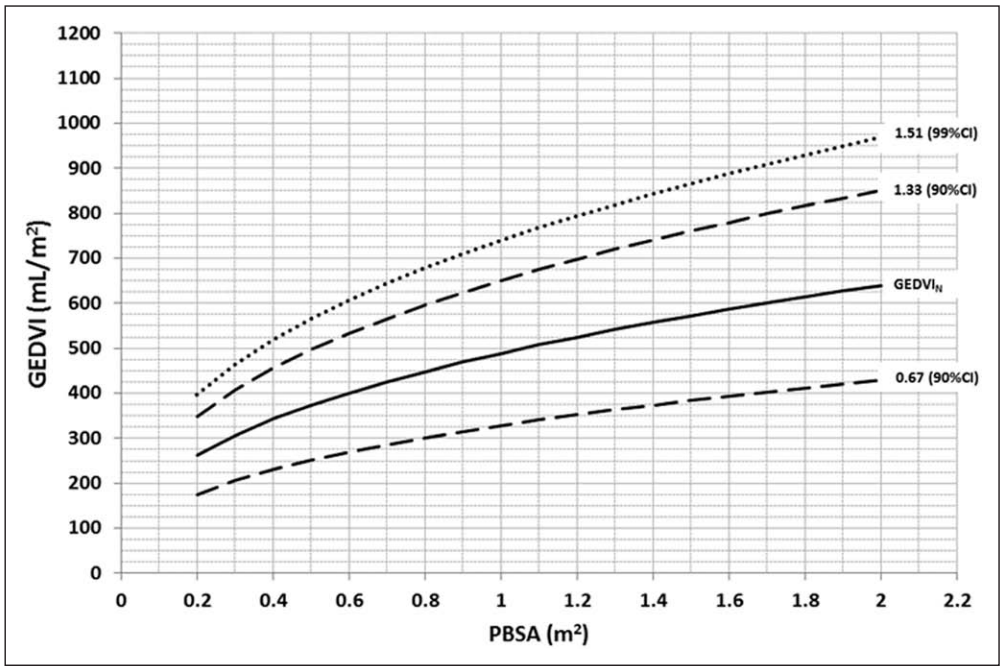

Figure 2. "Normal" global end-diastolic volume index (GEDVI) values in children. GEDVI versus predicted body surface area (PBSA) "normal" GEDVI ($GEDVI_N$) line was calculated from $GEDVI_N = 488.8 \cdot PBSA^{0.388}$. The lines corresponding to 0.67, 1.33, and 1.51 times $GEDVI_N$ were set according to 90% and upper 99% $GEDVI_N$ CIs, respectively, and define four levels of GEDVI-based cardiac preload.

consistent both in magnitude (ΔSVI) and rate of responsiveness, and $\Delta GEDVI/GEDVI_N$ was at its minimal level, indicating that the maximum cardiac end-diastolic volume had been reached. Additionally, SVI was at its maximum between 1.33 and 1.51 times $GEDVI_N$, indicating that the subjects were operating at maximum efficacy of the Frank-Starling response with no additional preload reserve.

In patients with dilated cardiomyopathy, $GEDVI/GEDVI_N$-SVI (CI) curves shift downward as expected from their reduced myocardial contractility. Although their slopes are lower than in the cardiovascular dysfunction group, they still keep a well-defined steep part below 1.33 times $GEDVI_N$ as supported by the fact that 75% of the fluid infusion observations with preinfusion preload status less than 1.33 times $GEDVI_N$ responded with an increase in SVI greater than 15% (Fig. 1) even though the median of the infused volume were as low as 5.8 mL/kg. It is not possible to conclude that there is an absence of fluid responsiveness above 1.33 times $GEDVI_N$ because although none of the three patients responded to volume infusion, the median volume infused was too low (median, 3.3 mL/kg) to consistently increase cardiac preload. However, the 8% drop in SVI above 1.51 times $GEDVI_N$ (Fig. 3) suggests afterload mismatch due to the limit of preload (Frank-Starling) reserve had been reached (32).

Pulmonary edema is an expected consequence of high preload, especially in the failing heart (33). EVLWI can detect small (10–20%) increases in lung water (34). EVLWI greater than 10 mL/kg is associated with pulmonary edema (35) and greater than 14 mL/kg with increased mortality in critically ill adults patients (10). EVLWI is higher in children than in adults, and values associated with pulmonary edema are still to be determined (28). In pediatric patients with respiratory failure, Lubrano et al (36) found that EVLWI remained higher than 23 ± 9 mL/kg in nonsurvivors and lower than 17 ± 8 mL/kg in survivors. According to our results, in the cardiovascular dysfunction group with a cardiac preload status below 1.33 times $GEDVI_N$, the EVLWI upper limit of the 95% CI is 16 mL/kg. By contrast, the EVLWI lower limit of the 95% CI is 19 mL/kg between 1.33 and 1.51 times $GEDVI_N$ and 22 mL/kg above 1.51 times $GEDVI_N$, supporting our conclusion that above 1.33 times $GEDVI_N$ the heart is functioning in the "flat" part of the Frank-Starling curve (Fig. 3) where it is known that fluid loading has little effect on CO and only serves to increase lung tissue edema (37). Accordingly, Aman et al (6) recently found that the plateau of CI rather than permeability or pressures predicted a ΔEVLWI greater than 10% during fluid loading in presumed hypovolemic critically ill patients, independent of the presence of sepsis and the volume and type of loading fluid.

This study has some limitations. Most of the patients did not have an echocardiogram at the time of the TPTD assessments, so we could not evaluate the impact of atrioventricular regurgitation on GEDVI. In addition, volume infusion may either increase intravascular blood volume (venous pooling) or interstitial fluid volume (capillary leak) but not necessarily affect cardiac preload (38, 39). Therefore, $GEDVI/GEDVI_N$-SVI (CI) curves allow assessment of a patient's preload responsiveness provided that a sufficient amount of the infused volume is able to reach the heart.

The increase in SV in response to an increase in cardiac preload depends mainly on the slope of the Frank-Starling curvilinear relationship which is influenced by afterload. In our study, there were no significant differences for SBP—a surrogate of afterload in the absence of aortic or pulmonary stenosis (40)—between the four preload status levels. Accordingly, a SBP beyond the limits of our study may affect the prediction of cardiac preload responsiveness based on the $GEDVI/GEDVI_N$-SVI (CI) relationships.

There is also the concern regarding possible mathematical coupling between the GEDV and CO. Michard et al (8) observed a positive relationship between changes in GEDVI and mean arterial pressure, two variables that cannot be mathematically coupled. We did not observe significant differences in SBP and MBP between the different preload levels, possibly because catecholamines were used to maintain normal blood pressure. However, our data show that the SVI stops increasing when the

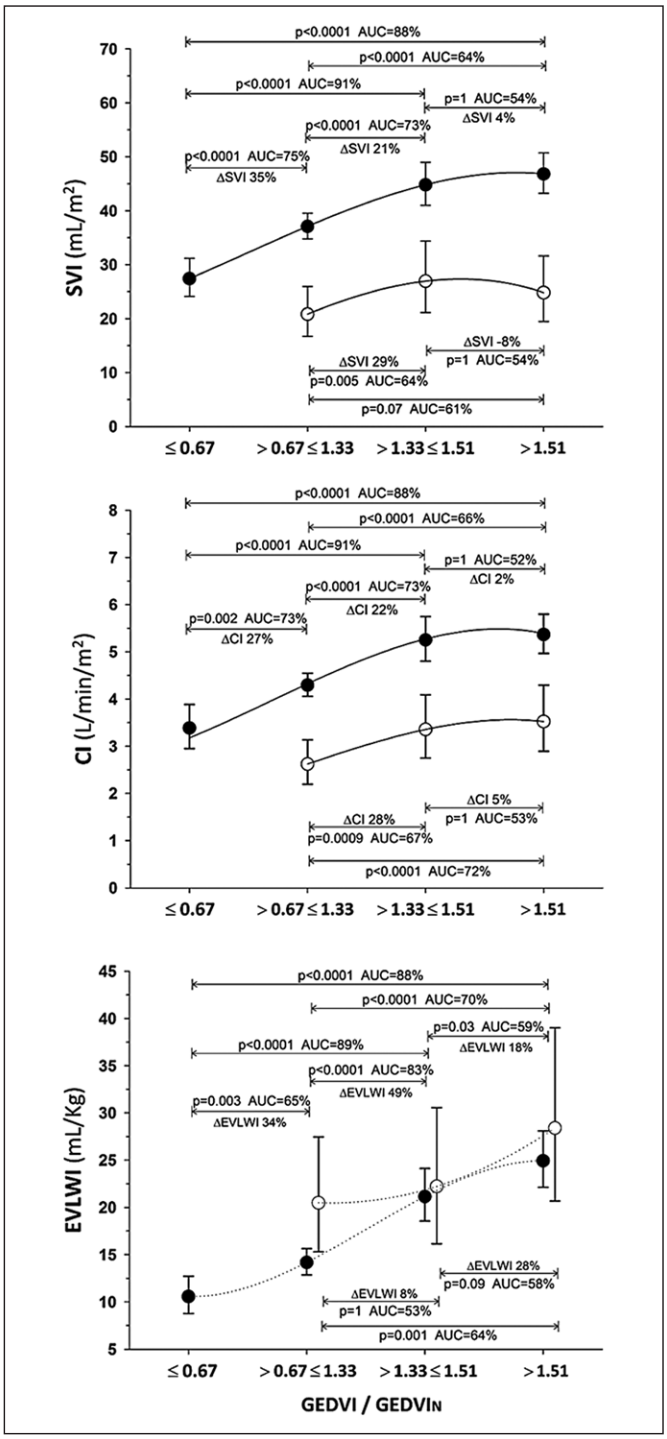

Figure 3. Normalized cardiac preload (global end-diastolic volume index [GEDVI]/normal global end-diastolic volume index [$GEDVI_N$]) versus stroke volume index (SVI), cardiac index (CI), and extravascular lung water index (EVLWI) in patients with cardiovascular dysfunction (*black circles*) and dilated cardiomyopathy (*white circles*). Data are geometric mean with error bars corresponding to 95% CIs. Second-order polynomial curves were used to fit data points. SVI and CI graphs emulate Frank-Starling curves with their steep and plateau phases. The highest EVLWI values are linked with the plateau phase. Area under the receiver-operating characteristic curve (AUC) represents the probability that a randomly selected subject with a defined cardiac preload status ($GEDVI/GEDVI_N$) will exhibit a different hemodynamic response (higher SVI, CI, or EVLWI) than a randomly selected subject with a lower preload status; minimum AUC = 0.5. $GEDVI/GEDVI_N$ = normalized GEDVI, ΔCI = % CI change, ΔEVLWI = % EVLWI change, ΔSVI = % SVI change.

GEDVI exceeded 1.33 times $GEDVI_N$, a response more in keeping with cardiac physiology than with mathematical coupling.

As with most of the observational pediatric studies with a wide range of ages and disease origins, several confounding factors may have distorted our results. Noncardiogenic pulmonary edema could have contributed to the EVLWI increase in some patients. Patients with cardiovascular dysfunction are a heterogeneous group in regard to the origin of shock, dose of catecholamines, ventilatory assistance, and the time course of disease, all of which may affect cardiac preload responsiveness, afterload, and pulmonary edema. The inhomogeneity in the types of fluids used (NS, HS3%, Ab5%, FFP, PRBCs, platelets) and in the duration of the infusion of the fluid challenges and volume loadings may have affected the results of fluid responsiveness shown in Figure 1. However, the sample we studied represents the complex PICU population with hemodynamic instability, a situation which physicians face on a daily basis.

CONCLUSIONS

This study provides "normal" values for GEDVI and limits of cardiac preload responsiveness in pediatric patients with cardiovascular dysfunction and dilated cardiomyopathy: 1.33 times $GEDVI_N$ represents the upper limit of cardiac preload responsiveness, with the highest expected responsiveness being below 0.67 times $GEDVI_N$. The maximum efficacy of the Frank-Starling response and therefore of no additional preload reserve is expected between 1.33 and 1.51 times $GEDVI_N$. Above 1.51 times $GEDVI_N$ preload responsiveness is very unlikely, and the risk of lung edema is maximal.

Further studies are needed to determine if the relationship between $GEDVI/GEDVI_N$ and SVI, CI, and EVLWI assist in decision making regarding volume loading in hemodynamically unstable children who need their CO optimized while avoiding the risk of fluid overload and pulmonary edema.

ACKNOWLEDGMENTS

We thank Prof. RM Kacmarek for his valuable assistance in writing this article. We gratefully acknowledge the assistance of the medical and nursing staff of the PICUs of the Hospital Universitario Infantil La Paz, Hospital Universitario Niño Jesús, Hospital Universitario Ramón y Cajal, Hospital Universitario Carlos Haya, Hospital Clínico Universitario de Valencia, Hospital Universitario 12 de Octubre, and Hospital Universitario Reina Sofía.

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