

Diagnostic accuracy of echocardiographic measurements as predictors of fluid responsiveness in mechanically ventilated children: a systematic review and meta-analysis

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ABSTRACT

Objective: To assess the accuracy of aortic blood flow peak velocity (ΔV_{peak}), and inferior vena cava variation (ΔIVCD) for diagnosis of fluid responsiveness in mechanically ventilated children with cardiovascular failure.

Data Sources: We searched MEDLINE, Scopus, and Cochrane Library from inception to November 2015.

Methods: Studies were included if patients aged 18 or younger and on control ventilation. Studies tests were ΔV_{peak} and ΔIVCD whereas fluid responsiveness, diagnosed by stroke volume, stroke volume index, cardiac index, or aortic velocity-time integral, were the outcome of interest. Diagnostic performances were pooled using a bivariate mixed-effect logit analysis and hierarchical summary receiver operating curves (HSROC) analysis.

Results: Nine studies (n = 250 patients) were included in pooling of ΔV_{peak} .

Pooled sensitivity, specificity, and likelihood ratio positive (LR+) were 0.86 (95% CI: 0.76, 0.93), 0.87(0.78, 0.93), and 6.5 (3.70, 11.70), respectively. These corresponding values for ΔIVCD were 0.85 (0.72, 1.00), 0.45 (0.10, 1.00), and 2.68 (0.25, 28.51), respectively. The area under SROC curves (AUSROC) for both tests were 0.93 (0.90, 0.95) and 0.66 (0.43, 0.89), respectively. Subgroup analysis for ΔV_{peak} cutoff 7%-12% yielded higher performances with sensitivity, specificity, LR+, and AUSROC of 0.94 (0.74, 0.99), 0.87 (0.68, 0.95), 7.1 (2.6, 19.9), and 0.96 (0.94, 0.97).

Conclusions: ΔV_{peak} , especially the cutoffs of 7% to 12%, has very good diagnostic performances in the prediction of fluid responsiveness in ventilated children with shock. Nevertheless, the pooled estimate of ΔIVCD is based on a small number of studies and subjects, more data are needed to confirm.

Abbreviations

CI, cardiac index; Δ IVCD, respiratory variation in inferior vena cava diameter; Δ V_{peak}, respiratory variation in aortic blood flow peak velocity; QUADAS, the Quality Assessment of Diagnostic Accuracy Studies; SVI, stroke volume index.

Introduction

Shock is defined as the state of circulatory dysfunction, in which the metabolic demands of the tissue cannot be met by the circulation. The first line of treatment is hemodynamic resuscitation, including adequate fluid therapy and oxygenation [1]. However, unsuitable fluid therapy (e.g., excessive or inadequate fluid infusion) can lead to poor clinical outcomes, e.g., pulmonary edema, acute heart failure and increased mortality [2-4]. In children, the optimization of fluid therapy is difficult to achieve. The signs of hypoperfusion from circulatory failure (e.g., capillary refill and skin perfusion) are more subtle in children than in adults and only 50% of patients with hemodynamic instability respond to fluid loading [5]. As a result, more reliable tools are required to identify patients who are most likely to respond to fluid expansion.

Numerous hemodynamic parameters to predict fluid responsiveness including static and dynamic variables have been proposed. Static variables (e.g., central venous pressure (CVP), or pulmonary capillary occlusion pressure) are poor to guide fluid therapy [6] whereas dynamic variables appear to be more accurate in evaluating fluid responsiveness in ventilated patients [7, 8]. A number of studies supported the accuracy of respiratory variation in aortic flow peak velocity (ΔV_{peak}), and respiratory variation in the inferior vena cava diameter ($\Delta IVCD$) using transthoracic or transesophageal echocardiography to predict fluid responsiveness in adults [9, 8, 10-12] but only a few in children. The first systematic review in children did not provide quantitative pooling due to the limited number of studies and diversity of study characteristics [13]. A more recent systematic review and meta-analysis [14] estimated diagnostic performances of only ΔV_{peak} by pooling 6 studies. They found that ΔV_{peak} was accurately predict fluid responsiveness in children. Since then, some additional studies have been published and an additional parameter, i.e., $\Delta IVCD$ has

also been studied. We, therefore, conducted a systematic review which aimed to update the diagnostic accuracy of ΔV_{peak} , and determine the performance of $\Delta IVCD$ in predicting fluid responsiveness in ventilated children with shock.

Methods

Search Strategy

Electronic databases were searched for relevant studies, using search terms based on ΔV_{peak} , $\Delta IVCD$, and fluid responsiveness. Searching was divided into three stages. First, all previous systematic reviews were identified from the Cochrane database of systematic reviews concerning fluid responsiveness in children were reviewed. Next, MEDLINE and Scopus (using PubMed and Scopus search engines) were used to locate relevant studies from the inception of each database until 15th November 2015. Finally, additional searching of the reference lists of the retrieved articles were reviewed. Use of search terms were as follows: “children” OR “pediatric*”, “variation in aortic blood flow velocity” OR “delta V_{peak} ”, “variation in inferior vena cava” OR “delta $IVCD$ ”, “stroke volume” OR “cardiac index”, “fluid respon*” OR “volume respon*”, “mortality”, “organ failure”.

Study Selection/Eligibility Criteria

Studies were selected independently by two authors (S.E and S.A.V.) based on titles, abstracts, and full papers. For studies with multiple publications, we selected the publication with the most relevant and complete data. Disagreement between reviewers was resolved by consensus and discussion with a third party (A.T.). Studies were included if they met the following criteria: patients aged 18 years or younger who were on mechanical ventilations in controlled modes, had ΔV_{peak} , or $\Delta IVCD$ measured by transthoracic or transesophageal echocardiography, and had the

reference test as stroke volume (SV), stroke volume index (SVI), cardiac index (CI), or aortic velocity-time integral (VTI) for the diagnosis of fluid responsiveness. Case reports, expert opinions, and reviews were not eligible. Studies with insufficient data for pooling were excluded after three attempts to contact authors.

Index tests

The ΔV_{peak} and $\Delta IVCD$ were measured according to original studies using transthoracic or transoesophageal echocardiography. The ΔV_{peak} was determined from the pulsed Doppler wave during beat-to-beat over a single respiratory cycle, and from the subcostal long axis view. It was measured approximately 1-3 cm from the right atrium by M-mode [15]. Figure 1 shows detail about how to measure ΔV_{peak} , $\Delta IVCD$.

The ΔV_{peak} was calculated as follows:

$$\Delta V_{peak}(\%) = \frac{(V_{peak\ max} - V_{peak\ min})}{\left(\frac{V_{peak\ max} + V_{peak\ min}}{2}\right)} \times 100$$

The respiratory variation in IVC^{15, 16} was calculated as follows:

$$\Delta IVCD(\%) = \frac{(IVCD\ max - IVCD\ min)}{\left(\frac{IVCD\ max + IVCD\ min}{2}\right)} \times 100$$

The interpretation of these index tests were categorized as positive or negative to fluid responsiveness according to individual studies' cutoffs.

Reference test

In current literature, the reference tests for defining fluid responsiveness could be any of 4 parameters: SV, SVI, VTI, and CI [16, 17, 7, 18]. The SV, an amount of blood pumped out of the

left ventricle to body estimating by the measurement of aortic annulus diameter (D), measured during systole in the parasternal long-axis view. Aortic velocity time integral (VTI) measured from an apical five-chamber view or a subcostal view by pulse Doppler.

The SVI was calculated as follows:

$$SVI = \frac{VTI \times \frac{\pi D^2}{4}}{BSA}$$

The CI was calculated as follows:

$$CI = SVI \times HR$$

SVI is measured as SV divided by body surface area (BSA). CI is calculated by multiplying SVI with heart rate (HR). Fluid responsiveness was defined accordingly to individual studies, but generally SV, SVI, VTI or CI \geq 10-15% after fluid loading was defined as fluid responsiveness [19].

Data Extraction

Two reviewers (S.E. and T.A.) independently extracted data using a standardized extraction form. The following study characteristics were extracted: clinical settings, sample size, types and duration of fluid loading, ventilator settings, average ages, weights, and instruments used for measuring index tests. We also extracted data for the parameters of interest (ΔV_{peak} , and $\Delta IVCD$), reference tests, 2x2 contingency table of $\Delta V_{peak}/\Delta IVCD$ and fluid responsiveness to calculate true positive, false positive, true negative, and true negative. If the data on 2x2 tables were insufficient, we sent three emails to the corresponding authors to request additional data. If the author did not respond to the emails, the study was excluded from the final analysis. Any disagreement on extraction of data was resolved by discussion or consensus with the senior authors.

Risk of Bias Assessment

Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist [20]. The QUADAS-2 consists of four domains: patient selection, index test, reference standard, and flow-timing. Each domain was assessed in terms of the risk of bias and the first three domains were also assessed in terms of applicability. Risk of bias was judged as “low”, “high”, or “unclear”. Each domain was judged as low risk if all signaling questions were answered “yes”, otherwise it was judged as high risk of bias. The “unclear” category was used only when insufficient data were reported to permit a judgment.

Statistical Analysis

A bivariate mixed-effect logit regression was applied to estimate diagnostic performances [21]. This method accounts for correlation between sensitivity and specificity, and thus a threshold or cut-off effect was also assessed and estimated [22]. The overall pooling of sensitivity, specificity, diagnostic odds ratio (DOR), likelihood ratio positive (LR^+), and likelihood ratio negative (LR^-) were estimated and reported along with their 95% confidence intervals (CIs). Hierarchical summary receiver operating curve (HSROC) analysis, which provides estimates of the variance of the log DOR, taking into account for threshold effect by estimating threshold coefficient, was used to construct summary receiver operating curves (SROC) of fluid responsiveness for each index tests [23, 24]. In addition, a Fagan nomogram was constructed by plotting LR^+ and estimated post-test probability of fluid responsiveness. For those studies that did not provide a 2x2 cross-tabulation of data but reported area under ROC along with 95% CI, the area under ROC was pooled using a previous method [25].

Heterogeneity across studies was assessed using the Cochrane Q statistic, and degree of heterogeneity (I^2). There was a significant I^2 if the p-value of Cochrane Q test was less than 0.1 [26] or I^2 was higher than 25%. A meta-regression was performed by fitting covariates (e.g., volume of fluid expansion, exclusion criteria for arrhythmia, congenital heart disease, and low ejection fraction) on ln (DOR). A subgroup analysis was performed accordingly if there was any suspected source of heterogeneity. Publication bias was assessed using Deeks' funnel plot with superimposed regression line [27], and the P-value for the slope coefficient was reported. Data were analyzed using STATA version 14.1 (StataCorp LP, College Station, TX, USA). A two-tailed P-value < 0.05 was considered statistically significant.

Results

Summary of the studies

Identification of relevant studies is summarized in Figure 2. A total of 1,673 articles were identified, 1,656 articles from MEDLINE and Scopus, and additional 6 and 11 articles from previous systematic reviews and reference lists, respectively. After the removal of duplications, 1,573 studies were included in the review process, leaving 10 eligible studies [28-37] for quantitative analysis. A total of 9 studies of ΔV_{peak} [31, 30, 32, 34, 36, 29, 28, 35, 33] and 2 studies of $\Delta IVCD$ [37, 35] fulfilled the inclusion criteria.

The main characteristics are summarized in Table 1. Two hundred and eighty one patients were included in the analysis. Mean age ranged from 16.2 to 72.1 months. More than a half of total studies (6 of 10 studies [28-31, 33, 36]) defined fluid responsiveness as increasing value of 15% or

higher, whereas the remainder used 10%. Six studies [28, 29, 33-35, 37] were set in intensive care, and 4 studies [30-32, 36] in the operating room. The amount of fluid loading ranged from 10 to 20 ml/kg/dose, and more than half of total studies [29, 31-33, 36, 37] started volume expansion at 10 ml/kg. Seven studies [29, 31-33, 36, 37] used colloid (6% hydroxyethyl starch) for fluid expansion. About the ventilator setting, 6 studies [29, 31-33, 36, 37] set a mean tidal volume of 10 ml/kg. Mean positive end-expiratory pressures (PEEPs) ranged from 0 to 6.8 cmH₂O, and 7 studies [28-33, 36] used PEEP \leq 5 cmH₂O. The majority of studies [28, 29, 31-33, 37] excluded patients who had arrhythmia, and/or congenital heart disease.

Risk of bias assessment

Risk assessment was performed following the QUADAS-2 checklist. The results of risk assessment and applicability are reported (Figure 3). For the first domain of patient selection, most studies were at low risk of bias, 8/10 studies [28-33, 36, 37] using a consecutive or random sample of patients, and clearly described the selection criteria. For the index test, although the majority of studies conducted and interpreted the index test in a similar way, 8 studies [28-33, 36, 37] had not specified a threshold prior to the start, and 2 studies [34, 35] unclearly reported this respect. Therefore, the index tests had a high risk of bias. More than half of all studies described the reference tests unclearly. Only 4 studies [29-31, 36] mentioned that they interpreted their results without knowledge of the results of the index test. For the last domain, flow and timing, all studies performed index and reference tests on the same patients, and the same reference standard was applied to all patients, but 3 studies [32, 34, 35] were unclear about timing of measuring index and reference tests. As for applicability, all studies were judged to have low concerns. Agreement for assessing risk of bias between the two reviewers was substantial with a *k* of 0.81 [38].

ΔV_{peak} performance

Nine studies [28-36] (n = 250 patients) were included in pooling of ΔV_{peak} diagnostic performances. Their performances and use of cut-offs for individual studies (varied from 7 to 20%) are described in Table 2. The pretest probability of fluid responsiveness was 0.57, Pooled sensitivity and specificity were 0.86 (95% CI: 0.76, 0.93) and 0.87(95% CI: 0.78, 0.93), respectively (Figure 4). The two diagnostic parameters (i.e., sensitivity and specificity) were incorporated and simultaneously pooled, which yielded DOR, LR+, and LR- of 41.76 (95% CI: 15.09, 115.53), 6.5 (95% CI: 3.70, 11.70), and 0.16 (95% CI: 0.09, 0.29) respectively. There was no evidence of a threshold (or cutoff) effect (Spearman correlation coefficient = -0.29; P = 0.53)

Although the I^2 s for LR+ and LR- were low to moderate, it was as high as 80.70 (95% CI: 68.81, 92.59) for the pooled DOR. Therefore, we performed meta-regression for identifying the potential source of heterogeneity. Subgroup analyses were performed (see Table 3), degrees of heterogeneity decreased to 62, 56.2, 46.6, 0, and 0 for pooling studies without arrhythmia [28, 29, 31-33, 36], congenital heart disease (CHD) [28, 29, 32, 33, 36], severe low ventricular function [28, 29, 32, 33], the cut offs of reference tests $\geq 15\%$ for defining fluid responsiveness [28-31, 33 36], and ΔV_{peak} cutoff 7%-12%, respectively. Results suggested that studies with the reference cut-off $\geq 15\%$ had higher pooled DOR of 80 (95%CI: 18, 352) than that of overall studies. This similar trend also found in pooling studies with ΔV_{peak} cut-offs 7% to 12% had improved diagnostic performances with DOR of 109 (95%CI 10, 1197)), and area under SROC of 0.96 (95%CI: 0.94, 0.97).

From all relevant studies, applying HSROC analysis yielded an area under SROC of 0.93 (95% CI: 0.90, 0.95) (Figure 5). A Fagan nomogram was constructed to estimate the post-test probability based on the pooled LR^+ of 7 and LR^- of 0.16. Given a pretest probability of 0.57 estimating across our studies, and the pooled LR^+ of 6.5, this yielded a post-test probability of fluid responsiveness of 0.90 if the ΔV_{peak} was positive (i.e., ranged from 7% to 20%) (Figure 6).

Publication bias was assessed using Deek's regression test of asymmetry. The plot suggested symmetry of the funnel of DORs across 9 studies using ΔV_{peak} . The estimated coefficient of bias was 3.29 (SE = 24.14, $p = 0.90$), which indicated low evidence of publication bias.

$\Delta IVCD$ performance

There were 4 studies mentioned about $\Delta IVCD$ [29, 32, 37, 35], but only 2 [37, 35] studies provided sufficient data for pooling (Table 4). The pooled sensitivity, specificity, LR^+ were 0.85 (95% CI: 0.72, 1.00), 0.45 (95% CI: 0.10, 1.00), and 2.68 (95% CI: 0.25, 28.51), respectively. The area under the ROC curves were reported from all 4 studies [29, 32, 35, 37], and ranged from 0.37 to 0.87; the pooled area under ROC was 0.66 (95%CI: 0.43, 0.89).

Discussion

We performed a systematic review and meta-analysis to estimate the diagnostic performance of 2 dynamic echocardiographic parameters, ΔV_{peak} and $\Delta IVCD$, in predicting fluid responsiveness in mechanically ventilated children with shock. The performance of ΔV_{peak} was excellent but not for $\Delta IVCD$, with sensitivity, specificity, LR^+ , LR^- , and AUSROC were 86%, 87%, 6.54, 0.16, and 0.93, respectively. According to the Users' Guide to Evidence-Based Medicine, diagnostic tests

[39] with LR+ of 5-10 and the LR- of 0.1-0.2 would be able to moderately shift pre-test probabilities and should be able to assist in clinical practice if that test is not invasive and available in routine care. The overall performance of ΔV_{peak} was good but it was poor for $\Delta IVCD$, with the LR+ and AUROC of 6.54 and 0.93 for ΔV_{peak} , and 2.68 and 0.66 for $\Delta IVCD$.

The previous meta-analysis [14] included 6 studies enrolling a total of 163 patients and reported the pooled sensitivity, specificity, DOR, and SROC as 92.0%, 85.8%, 50.44 (95% CI: 17.70, 143.74), and 0.94 respectively. Our studies had added 3 more studies with similar results. In addition, we have also constructed Fagan nomogram, which should be helpful in clinical practice to estimate the post-test probability of fluid responsiveness. Our results are also similar to results of adult study [10] which suggested that ΔV_{peak} of 12% could well predict fluid responsiveness.

ΔV_{peak} is one of the dynamic indices used for assessing fluid responsiveness based on estimation of preload dependence from heart-lung interaction under mechanical ventilation, and deep sedation [40]. However, its performances much depend on its cutoff and also reference test's cutoff. For instance, the ΔV_{peak} cutoff 7% to 12% yielded better performances than the cutoff $> 12\%$; the reference test $\geq 15\%$ was better performances than $< 15\%$. Most studies excluded patients with arrhythmias, low EF, and CHD. The presence of cardiac arrhythmias can lead to misinterpretation of respiratory changes in aortic blood flow from the irregularity of diastolic phase [41]. The next condition is cardiac function. When there is a reduction in cardiac contractility, right atrial pressure (RAP) will rise resulting in the cardiac function curve or Frank-Starling curve moving to the right [42]. As a result, the accuracy of prediction of fluid responsiveness in children with arrhythmias, and abnormal cardiac contraction can be affected. Concerning congenital heart disease, 5 included studies [28, 29,

32, 33, 36] excluded patients with CHD from their studies. The pooled data from this group yielded the high AUROC of 0.90. However, Renner and colleagues [31] included 27 children from elective cardiac surgery. The measurements were performed under closed chest conditions before the surgical correction, and AUC was 0.92 (95% CI: 0.80, 1.00), but many cases had simple lesions of CHD (e.g., secundum atrial septal defect, ventricular septal defect, and atrioventricular septal defect). For the setting of mechanical ventilator, especially PEEP, and tidal volume, magnitude of these factors can change in left ventricle volume [43], which can affect the accuracy of test to predict fluid responsiveness. In our meta-analysis, PEEP and tidal volume ranged from 0 to 6.8 cmH₂O and 7.4 to 10 mL/kg, respectively. We performed subgroup analyzed of these two factors. However, there was no definitive conclusion which can be drawn in these subgroups because of too small number of studies. Therefore, the impact of PEEP and tidal volume on the diagnostic performance of ΔV_{peak} needs to be validated in further studies.

For $\Delta IVCD$, the pooled LR⁺ was only 2.68, which is too small to be useful in routine clinical practice. However, this finding is based on pooling a small number of included studies.

Contrastingly, systematic review of adult data [9] indicated good performances in predicting fluid responsiveness, especially in patients on controlled mechanical ventilation. Thus, this meta-analysis of $\Delta IVCD$ needs to be updated when more pediatric data are available.

However, there are some limitations in our study. Firstly, diagnostic performances were pooled based on aggregated data and the ΔV_{peak} cutoff varied, following the original individual studies. Re-classification using the same cutoff across all included studies would require individual patient data. Secondly, the index domain in QUADAS-2 is estimated to have high risk of bias because the

threshold of ΔV_{peak} across all studies was not prespecified, leading to a probable overestimate in the test performance [44]. Finally, the available data of $\Delta IVCD$ in our study were limited resulting in an inability to fully investigate diagnostic performance of this dynamic variable in children.

Conclusions

In conclusion, ΔV_{peak} is a useful parameter of echocardiography in predicting fluid responsiveness in children with controlled mechanical ventilation. A positive ΔV_{peak} could lead to post-test probability of having fluid responsiveness of approximately 90%. This dynamic parameter can be measured by cardiac ultrasound technique, but if it is widely adopted, data should be generated regarding its intra- and inter-user reproducibility. As a result of the limitation of data for $\Delta IVCD$, the diagnostic performance of this parameter needs to be evaluated in further studies.

Competing Interests

The authors declare that they have no competing interests. No funding source supported for this review.

Authors' contributions

S.E. performed searching and selecting studies, data extraction, statistical analyses and interpretation, risk of bias assessment, and wrote the first draft the manuscript. S.A.V. performed selection of studies, critically revised manuscript, and supervise in clinical contents. T.A. performed data extraction and risk of bias assessment. A.I, J.A. and M.M critically commented and revised the manuscript. A.T. designed review methodology, performed statistical analyses and interpretation, writing manuscript, and supervision of the whole study. All authors have approved the manuscript.

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Figures Legends

FIGURE 1: Echocardiographic measurements of ΔV_{peak} , and $\Delta IVCD$. a. Measurement of ΔV_{peak} , b. Measurement of $\Delta IVCD$. $IVCD_{max}$, the maximum diameter of inferior vena cava; $IVCD_{min}$, the minimum diameter of inferior vena cava; $V_{peakmax}$, the maximal diameter of aortic peak velocity, $V_{peakmin}$, the minimum diameter of aortic peak velocity.

FIGURE 2: Flow diagram for identifying and selecting studies for ΔV_{peak} , and $\Delta IVCD$.

FIGURE 3: QUADAS-2 risk of bias and applicability assessment.

FIGURE 4: Forest plots of sensitivity and specificity of respiratory variation in aortic blood flow peak velocity (ΔV_{peak}) for prediction of fluid responsiveness.

FIGURE 5: Summary receiver operating characteristic curve. AUC, area under the curve; SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating characteristic.

FIGURE 6: Fagan nomogram of respiratory variation in aortic blood flow peak velocity (ΔV_{peak}) for diagnosis of fluid responsiveness.