

Diagnostic Accuracy of Transthoracic Echocardiography to Predict Fluid Responsiveness by Passive Leg Raising in the Critically Ill: A Meta-Analysis

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Abstract

Background: Hemodynamic instability is common in critical patients and not all patients respond to fluid challenge, so we need accurate and rapid hemodynamic techniques to help the clinicians to guide fluid treatment. Numerous hemodynamic techniques have been used to predict fluid responsiveness till now. Transthoracic echocardiography (TTE) appears to have the ability to predict fluid responsiveness, but there is no consensus on whether it can be used by passive leg raising (PLR). **Methods:** We performed a literature search using MEDLINE (source PubMed, from 1947), EMBASE (from 1974) and the Cochrane Database of Systematic Reviews for prospective studies with no restrictions. Pooled effect estimates were obtained by using random-effects meta-analysis. **Results:** 7 prospective studies involving 261 patients and 285 boluses were identified. The pooled sensitivity and specificity of TTE are 86% (79% - 91%) and 90% (83% - 94%), respectively. The summary receiver operating characteristic (sROC) curve shows an optimum joint sensitivity and specificity of 0.88, with area under the sROC curve (AUC) of 0.94. The result of diagnostic odds ratio (DOR) is 50.62 (95% confidence interval [CI]: 23.70 - 108.12). The results of positive likelihood ratio (+LR) and negative likelihood ratio (-LR) are 7.07 (95% CI: 4.39 - 11.38) and 0.19 (95% CI: 0.13 - 0.28), which indicated strong diagnostic evidence. **Conclusions:** TTE is a repeatable and reliable noninvasive tool to predict fluid responsiveness in the critically ill during PLR with good test performance. This meta-analysis brings evidence to employ well-trained clinician-echocardiographers to assess patients' volume status via TTE to benefit daily work in intensive care units (ICUs).

Keywords

TTE, PLR, Fluid Responsiveness, Meta-Analysis

1. Introduction

The management of the critically ill patient to optimization the tissue oxygen delivery is an essential part in intensive care unit (ICU). Insufficient intravascular loading in the early resuscitation of acute sepsis results in tissue under perfusion, organ dysfunction, and acidosis. Excessive fluid administration has also been shown to be detrimental in the perioperative setting and in acute lung injury, prolonging both time on mechanical ventilation and time in intensive care [1] [2]. However, it has been reported 50 percent of patients do not exhibit the desired effect after fluid bolus [3] and more than half of patients have the risk of excessive fluid administration [4]. It is therefore essential to have reliable tools for predicting the efficacy of volume expansion (VE) and thus distinguishing patients who might benefit from VE from those in whom the treatment is likely to be inefficacious.

For the past 10 years, many studies have focused on the prediction of fluid responsiveness. Static hemodynamic indices (such as central venous pressure [CVP] or pulmonary artery occlusion pressure [PAOP]) are demonstrated to be little value in predicting fluid responsiveness [5] [6]. Dynamic indices (such as stroke volume variation [SVV] or pulse pressure variation [PPV]), based on analysis of preload dependence, have been validated to predict fluid responsiveness [5] [7] [8] [9]. And now modern intensive care is increasingly concerned with the avoidance of unnecessary invasive procedures which contribute to patient morbidity either directly or more often through the associated risk of catheter-related bloodstream infection [10]. So, invasive or mini-invasive methods are replacing by new methods focused on non-invasive.

Passive leg raising (PLR) is a reversible maneuver that mimics VE by shifting venous blood from the lower limbs toward the intrathoracic compartment [11]. This provides a transient volume load of between 150 and 300 milliliters to the central circulation in one minute [12] [13]. Because the heart (left and right ventricles) works on the stiff portion of the Frank-Starling relationship, therefore PLR can increase cardiac preload as “auto-transfused” into the central circulation [11]. Transthoracic echocardiography (TTE) is increasingly used for noninvasive hemodynamic assessment of critically ill patients since high-quality images and Doppler signals are obtained with recent TTE equipment [14]. TTE provides clinicians with valuable information including stroke volume, left ventricular preload, and filling. The stroke volume can be easily obtained using the left ventricular outflow track Doppler method [21]. But there is no consensus on whether it is useful during passive leg raising. Accordingly, the aim of this study is to answer the question: Can transthoracic echocardiography to be used as a tool for predicting volume responsiveness in critically ill by PLR?

2. Methods

2.1. Study Selection

Two authors independently performed a search in MEDLINE (using PubMed as the search engine, from 1947), EMBASE (from 1974) and the Cochrane Database of Systematic Reviews for prospective studies with the following key words: ((transthoracic OR thoracic) AND (echocardiograph* OR echog* OR doppler)) AND “passive leg raising”.

Only full-text articles in indexed journals were included. Reviews, chapter, case reports, reference network and studies published in abstract form were excluded. No language restriction was imposed. We included only studies with adult patients admitted in ICU. Articles were collected by one reviewer and crosschecked by another reviewer and references of included papers were examined to identify other studies of interest.

2.2. Inclusion Criteria

We included full-text studies with the following criteria: 1) PLR was performed and followed with VE; 2) the number of patients and boluses had been counted; 3) the reference standard of predicting fluid responsiveness had been described; 4) sensitivity, specificity and the threshold of the index in identifying those patients who subsequently responded to VE had been calculated.

2.3. Data Extraction and Quality Assessment

Data extraction of all variables and outcomes of interest was performed independently by 2 authors independently. For all included studies, two authors extracted the following information by using a standardized form: authors, year of publication, study setting, population, age of patients, number of patients included, ventilation mode, cardiac rhythm (sinus vs. arrhythmias), type and amount of VE, time of VE, definition of responders, position, manufacturer of TTE, amount of VE administered, number and percentage of responders, sensitivity, specificity, best threshold and area under the ROC curve (AUC). Data reporting conformed to the Standards for Reporting of Diagnostic Accuracy (STARD) [15].

We use QUADAS-2 (quality assessment of diagnostic accuracy-2) [16] to assess the quality of included studies on diagnostic accuracy in systematic reviews. The checklist was structured with 4 parts: Patient selection, index test, reference standard and flow and timing.

2.4. Statistical Analysis

We used RevMan 5.2 (Cochrane Collaboration, Oxford, UK) to make the QUADAS-2 scale to assess quality of studies on diagnostic accuracy to be included in systematic reviews [17]. Using MetaDiSC 1.4 (Unit of Clinical Biostatistics team of the Ramon y Cajal Hospital, Madrid, Spain), we calculated pooled values of sensitivity, specificity, diagnostic odds ratio (DOR) and area under summary receiver operating characteristic

(sROC) curve with P-values of less than 0.05 considered statistically significant [18]. Publication bias was performed by STATA statistical software 12.0 (StataCorp, College Station, TX) [19].

3. Results

3.1. Article Search

The initial search yielded 345 articles, of which 93 articles were excluded for not directly concerning of this item. 122 articles were subsequently excluded for review, reference work and book. Based on the inclusion criteria, 65 articles were excluded. 58 articles were subsequently excluded for not using TTE. Finally, 7 full-text articles were included for meta-analysis [20]-[26].

3.2. Quality of Reporting and Study Characteristics

Characteristics of the 7 included articles are summarized in **Table 1** and the main results are reported in **Table 2**. The results of QUADAS-2 are showed in **Figure 1**.

All the included 7 studies (261 patients, 285 boluses) were prospective studies with critically ill patients in shock. 3 studies [21] [23] [24] enrolled patients with spontaneous breathing and in sinus rhythm. The others enrolled patients adapted to ventilator and in rhythm or arrhythmia. 2 studies [22] [26] took transthoracic Doppler ultrasound device (USCOM®) for hemodynamic monitoring and traditional transthoracic echocardiography was used by the other studies. In all, 261 patients (range 17 - 89 for single paper) enrolled. A total of 285 fluid boluses were administered. The mean responder rate was 53.9%.

Table 1. Characteristics of studies included in this meta-analysis.

Authors	Year	NO.	Ventilation	Rhythm	VE	Time	Position	Responder	Index	Device
Lamia [20]	2007	24	MV/SB	sinus/AF	500cc saline	over 15 min	semirecumbent position	$\Delta SVI \geq 15\%$	cVTIAo	TTE (Philips)
Maizel [21]	2007	34	SB	sinus	500cc saline	over 15 min	supine position	$\Delta CO \geq 12\%$	cCO cSV	TTE (Philips)
Thiel [22]	2009	89	MV/SB	sinus/arr	500cc saline Ringer's lactate hetastarch	-	semi-recumbent position	$\Delta SV \geq 15\%$	cSV	TTE (USCOM®)
Biais [23]	2009	30	SB	sinus	500cc saline	15 min	semi-recumbent position	$\Delta SV \geq 15\%$	cSV	TTE (Siemens)
Préau [24]	2010	34	SB	sinus	500cc HES	over 30 min	semi-recumbent position	$\Delta SV \geq 15\%$	cSV	TTE (Philips)
Guinot [25]	2011	17	MV	sinus/arr	500cc saline	15 min	semi-recumbent position	$\Delta SV > 15\%$	cSV cCO	TTE (Philips)
Wang [26]	2011	33	MV/SB	sinus/arr	500cc saline	15 min	semi-recumbent position	$\Delta SV \geq 15\%$	cSV	TTE (USCOM®)

MV, mechanical ventilation, arr, arrhythmia, AF, atrial fibrillation, VE, volume expansion, min, minutes, Δ , variation; c PLR induced changes in, CO, cardiac output, SV, stroke volume, VTIAo, aortic velocity-time integral, SVI, stroke volume index, TTE, transthoracic echocardiography, USCOM, transthoracic Doppler ultrasonography.

Table 2. Main results of studies included in this meta-analysis on TTE in predicting fluid responsiveness by PLR.

Authors	Index	Boluses	Rps %	AUC	Best threshold	r	Sens.	Spec.	DOR	+LR	-LR
Lamia [20]	cVTIAo	24	54	0.96	12.5	0.83	77	100	69	18	0.3
Maizel [21]	cSV	34	50	0.9	8		88	83	35	5	0.1
Thiel [22]	cSV	102	46	0.89	15		81	93	54	11	0.2
Biais [23]	cSV	30	67	0.92	16		85	90	51	9	0.2
Préau [24]	cSV	34	41	0.94	10	0.86	86	90	54	9	0.2
Guinot [25]	cCO	25	52	0.87	5	0.84	85	83	28	5	0.2
Wang [26]	cSV	36	67	0.95	15		100	83.3	206	5	0
Overall (95% CIs)		285	53.857				85.8	89.8	50.6	7.1	0.19
							(79.1 - 91.0)	(83.4 - 94.3)	(23.7 - 108.1)	(4.4 - 11.4)	(0.13 - 0.28)

AUC, area under the receiver operating characteristics curve, c PLR induced changes in, Rps, responders, 95% CIs, 95% confidence intervals, Sens, sensitivity, Spec, specificity, DOR, diagnostic odds ratio, +LR, positive likelihood ratio, -LR, negative likelihood ratio, SV, stroke volume, CO, cardiac output, VTIAo, aortic velocity-time integral.

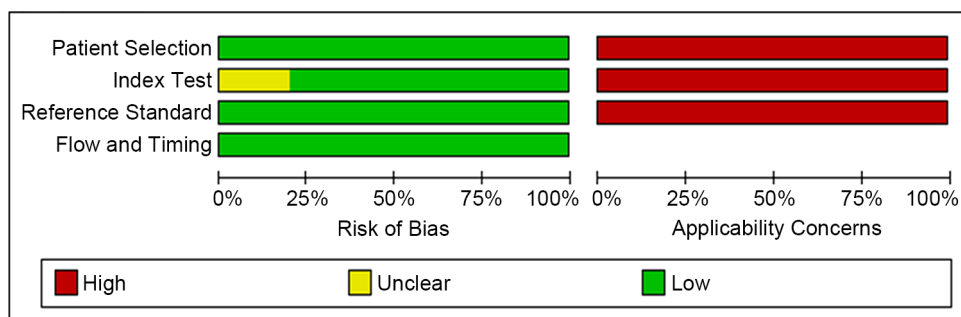


Figure 1. QUADAS-2 results of included studies on TTE in predicting fluid responsiveness by PLR (software RevMan 5.2).

3.3. Diagnostic Accuracy

Forest plots of the pooled sensitivity and specificity are shown in **Figure 2**.

The results $I^2 = 0.0\%$ ($<50\%$) and $p = 0.972$ (>0.05) showed that heterogeneity was not significant among the trials. The sensitivity ranged from 77% - 100% (pooled sensitivity 86%, 95% CI: 79% - 91%), while specificity ranged from 82% - 100% (pooled specificity 90%, 95% CI: 83% - 94%). The +LR was 7.07 (95% CI: 4.39 - 11.38), -LR was 0.19 (95% CI: 0.13 - 0.28), and DOR was 50.62 (95% CI: 23.70 - 108.12). Chi-square values for sensitivity, specificity, +LR, -LR, and DOR were 9.06 ($P = 0.17$), 4.74 ($P = 0.578$), 2.53 ($P = 0.865$), 3.14 ($P = 0.792$), and 1.29 ($P = 0.972$), respectively. These also indicated heterogeneity was not significant across studies regarding sensitivity, specificity, +LR, -LR, and DOR.

As shown in **Figure 3**, the sROC curve showing sensitivity versus 1-specificity from individual studies is not positioned near the desirable upper left corner. The maximum joint sensitivity and specificity was 0.88, with AUC of 0.94.

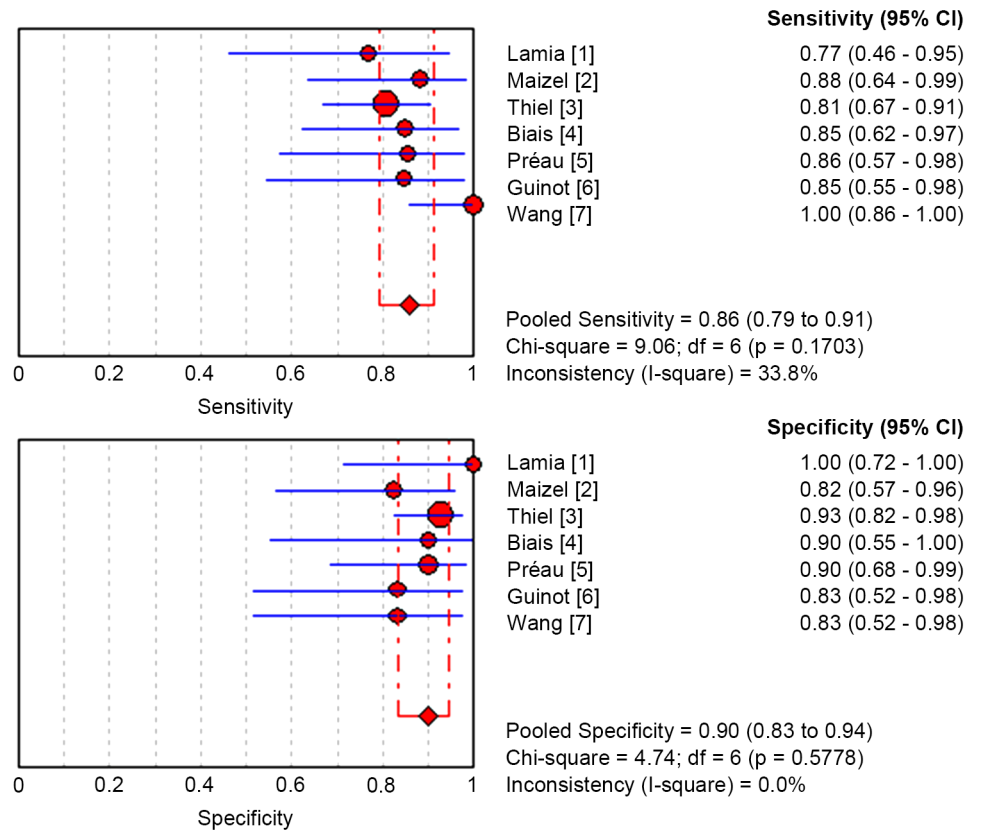


Figure 2. Forest Plots of Pooled Sensitivity and specificity of the included studies on TTE in predicting fluid responsiveness by PLR.

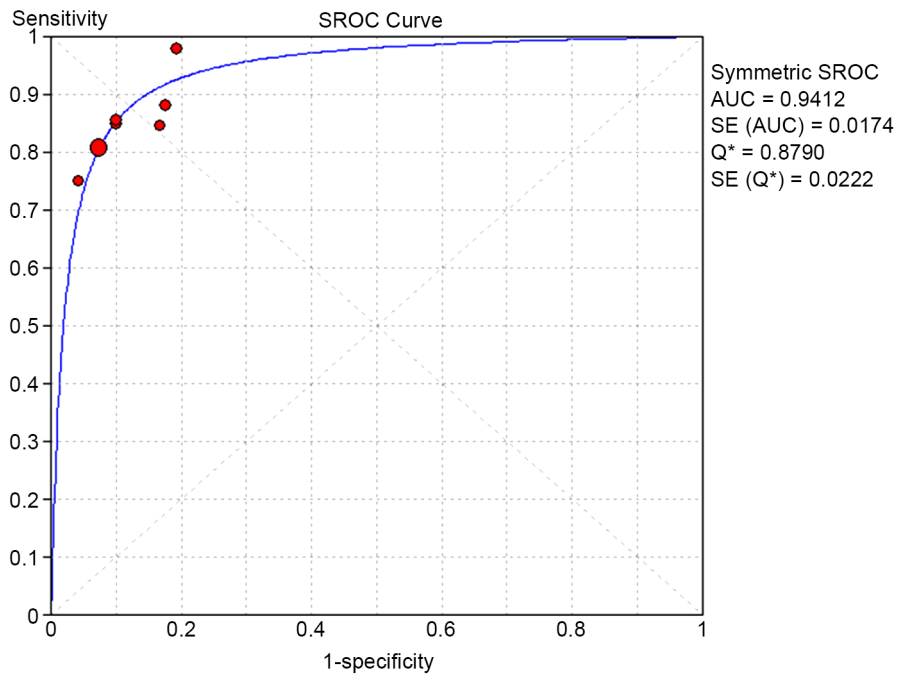


Figure 3. Summary Receiver Operating Characteristics Curve for the ability of TTE in predicting fluid responsiveness by PLR.

The Egger test and Begg test showed that the potential publication bias was significant ($P < 0.05$), which indicated a potential for publication bias. Due to the limited number of included studies in the meta-analysis, funnel plots were not assessed.

4. Discussion

The results of the present meta-analysis demonstrate that the pooled sensitivity and specificity of TTE are 86% (79% - 91%) and 90% (83% - 94%), respectively. The sROC curve shows an optimum joint sensitivity and specificity of 0.88, with AUC of 0.94, which indicates that TTE is good tool to be used to predict fluid responsiveness. The result of DOR is 50.62 (95% CI: 23.70 - 108.12), which indicates using non-invasive techniques have better discriminatory test performance with higher DOR values [8]; the results of +LR and -LR are 7.07 (95% CI: 4.39 - 11.38) and 0.19 (95% CI: 0.13 - 0.28). +LR above 5 and -LR below 0.2 have been noted as providing strong diagnostic evidence [27].

Passive leg raising (PLR) is a reversible maneuver that mimics rapid VE by shifting venous blood from the lower limbs to the intrathoracic compartment and introduces a reversible increase in preload of the right [28] and left ventricle [29]. TTE is a safe and convenient hemodynamic tool, which enable clinicians make fast assessment of patients' volume statue at the bedside, especially in patients with spontaneous breathing. In such patients, volume responsiveness is difficult to predict [30] [31]. TTE techniques appear useful in patients with spontaneous respiratory effort and those with arrhythmias: this is in contrast to many of the techniques that involve invasive monitoring which have been shown to be inaccurate in these situations [32]. But the operation of TTE really needs qualified clinicians. A good clinician can obtain the information from the TTE screen accurately.

A recent study by Mandeville *et al.* [33] concludes that TTE accurately predict fluid responsiveness in critically ill patients with discriminative power not affected by the technique selected. But the predictive value of TTE has not been evaluated yet. In this meta-analysis, it has been suggested that TTE could accurately predict fluid responsiveness by passive leg raising in the critically ill patients.

This meta-analysis has certain limitations. First, thoracic or abdominal wounds may sometimes make views impossible to achieve and obesity or rib prominence can also make TTE acoustic windows difficult to obtain. Second, TTE requires qualified clinician-echocardiographers through a defined training process, who can obtain information from the screen of TTE accurately and answer to the daily clinical conundrum of fluid responsiveness. Third, small size of the studies is included in this study with only a single study included 89 patients [20]. However, Zhang *et al* confirmed that small trials are more likely to report larger beneficial effects than large trials in critical care medicine, and Caution should be practiced in the interpretation of meta-analyses involving small trials [34]. Finally, the pooling of diagnostic accuracy data inevitably contribute to sources of bias [29], which are revealed in the significant amount of statistical heterogeneity across studies. As positive results of studies are more likely to be published,

publication bias may be introduced by inflation of diagnostic accuracy estimates.

TTE is a repeatable and reliable noninvasive tool to predict fluid responsiveness in the critically ill during PLR with good test performance. This meta-analysis gives evidence to bring up well-trained clinician-echocardiographers to assess patients' volume status via TTE to benefit daily work in ICUs.

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Conflicts of Interest

There are no conflicts of interest.

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