Value of Variation of End-Tidal Carbon Dioxide for Predicting Fluid Responsiveness During the Passive Leg Raising Test in Patients with Mechanical Ventilation: A Systematic Review and Meta-Analysis

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Research

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Abstract

Background: The variation of end-tidal carbon dioxide (ΔEtCO_2) has been extensively studied with respect to its value in predicting fluid responsiveness, but the results are conflicting. This meta-analysis aimed to explore the value of ΔEtCO_2 for predicting fluid responsiveness during the passive leg raising (PLR) test in patients with mechanical ventilation.

Methods: PubMed, Embase, and Cochrane Central Register of Controlled Trials were searched up to November 2021. The diagnostic odds ratio (DOR), sensitivity, and specificity were calculated. The summary receiver operating characteristic curve was estimated, and the area under the curve (AUROC) was calculated. We performed meta-regression analysis for heterogeneity exploration and sensitivity analysis for the publication bias.

Results: Overall, 298 patients were included in this review, of whom 149 (50%) were fluid responsive. The cutoff values of ΔEtCO_2 varied across studies, ranging from 5% to 5.8% or absolute increase 2 mmHg. Heterogeneity between studies was assessed with an overall $Q = 4.098$, $I^2 = 51\%$, and $P = 0.064$. The pooled sensitivity and specificity for the overall population were 0.79 (95% CI: 0.72–0.85) and 0.90 (95% CI: 0.77–0.96), respectively. The DOR was 35 (95% CI: 12–107) (Fig. 4). The pooled AUROC was 0.81 (95% CI: 0.77–0.84). On meta-regression analysis, the number of patients was sources of heterogeneity. The sensitivity analysis showed that the pooled DOR ranged from 21 to 140 and the pooled AUC ranged from 0.92 to 0.96 when one study was omitted.

Conclusions: This study was the first meta-analysis to evaluate the diagnostic accuracy of ΔEtCO_2 in predicting fluid responsiveness during PLR test in patients with mechanical ventilation. This study confirmed that the ΔEtCO_2 performed well in predicting fluid responsiveness in patients with mechanical ventilation.

Introduction

Fluid resuscitation is recommended and widely used as the first-line resuscitative therapy for all patients presenting with acute circulatory failure [1]. Although the volume status of a shocked patient is recovered, evidence suggests that inappropriate administration of fluids has deleterious effects such as volume overload, systemic and pulmonary edema, and limitation of oxygen diffusion to tissues, thereby leading to increased tissue hypoxia [2–4]. Therefore, it is important to obtain reliable information about fluid responsiveness in patients having a circulatory failure in the intensive care unit. However, clinicians are often faced with inaccurate, nonspecific information to guide their treatment.

Previous studies have shown that some parameters may be related to volume status. The traditional static parameters, such as intrathoracic blood volume index, pulmonary wedge pressure, and central venous pressure, have been proved not related to patient volume status [5, 6]. Hemodynamic parameters, such as pulse pressure variation and stroke volume variation, may better predict fluid responsiveness. However, the evaluation of these parameters requires invasive procedures and special monitoring equipment, limiting their clinical application [7].

End-tidal carbon dioxide (EtCO_2) is the partial pressure of carbon dioxide (PCO_2) in the exhaled air measured at the end of expiration. Measurement of EtCO_2 using capnography provides a noninvasive estimate of cardiac output and organ perfusion during cardiac arrest and can therefore be used to monitor the quality of cardiopulmonary resuscitation and predict return of spontaneous circulation [8–10]. In recent years, the variation of EtCO_2 (ΔEtCO_2) during passive leg raising (PLR) test or fluid challenge has been considered as a tool to help guide fluid resuscitation [11–17]. Physiologically, EtCO_2 depends on three variables: tissue CO_2 production, pulmonary blood flow (i.e. cardiac output), and alveolar ventilation [18]. Thus, EtCO_2 may accurately reflect cardiac output when ventilator parameters and CO_2 production are constant. This correlation has been tested in experimental [19] and clinical [20] studies. Therefore, it is theoretically possible to assess fluid responsiveness after PLR test or volume expansion according to ΔEtCO_2 if there is no major change in heart rate.

In this systematic review and meta-analysis, the test characteristics of ΔEtCO_2 were summarized as a predictor of fluid responsiveness during PLR test in patients with mechanical ventilation to elucidate their diagnostic performance further and provide information for the early detection of fluid responders.

Materials And Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidance [21].

Registration and protocol

This meta-analysis was registered on PROSPERO (CRD42021284241)

Search strategy

Relevant studies up to November 2021 were searched in the PubMed, Embase, and Cochrane Library databases with the following terms and their combinations: “fluid therapy OR fluid responsive OR volume responsive,” “end tidal carbon dioxide OR end-tidal carbon dioxide OR EtCO_2 ” and “mechanical ventilation OR ventilated.” All scanned abstracts, studies, and citations were reviewed. Moreover, references of the retrieved manuscripts were also manually cross-searched for further relevant publications.

Selection criteria

The inclusion criteria were as follows: (1) studies on patients receiving mechanical ventilation; (2) studies with PLR-induced increase in EtCO_2 as the index test; (3) studies with a gold reference standard for the diagnosis of fluid responsiveness; (4) studies published with full-text in any language; (5) studies providing

sufficient data for constructing 2-by-2 tables, including true positive (TP), false positive (FP), true negative (TN), and false negative (FN). The exclusion criteria were as follows: (1) studies that used the same population or overlapping database and (2) studies on animal models.

Data extraction and quality assessment

All the available data were extracted from each study by two investigators independently according to the aforementioned inclusion criteria, and any differences were resolved by discussion with a third investigator. The following data were collected from each study: (1) basic characteristics of studies, including first author name, publication year, country where the research was performed, selected patients, gender, mean age, number of patients, tidal volume, index test device for the EtCO₂, reference standard measurement, reference standard threshold, and reference standard device; (2) diagnostic performance, including cutoff value, sensitivity, specificity, area under the receiver operator characteristic curve (AUROC), TP, FP, FN, and TN. The quality of included studies was scored independently by two reviewers using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria [22]. The quality of studies was assessed using RevMan 5.4.

Statistical analysis

All analyses were performed using the Stata 16.0 software (Stata Corp., College Station, TX, USA). The bivariate meta-analysis model was employed to summarize sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR) [23, 24]. The sensitivity and specificity of each included study were used to plot the summary receiver operator characteristic (SROC) curve and calculate the area under the SROC curve (AUC). Diagnostic power was good, moderate, and poor if the AUC was more than 0.8, between 0.7 and 0.8, and less than 0.7, respectively [25]. As publication bias is a concern for meta-analyses, the Deeks' funnel plot asymmetry test was used, with $P \geq 0.10$ indicating statistical significance [26]. If publication bias was present, a sensitivity analysis was performed to explore why.

Spearman's correlation coefficient between the logit of sensitivity and logit of 1-specificity was calculated to determine any threshold effect; A strong positive correlation would suggest threshold effect [27]. The between-study heterogeneity was evaluated using Q test and I^2 statistics. A P value less than 0.10 for the Q test or I^2 value $\geq 50\%$ indicated substantial heterogeneity. A fixed effects model was used if no heterogeneity was observed. A random effects model was selected if significant heterogeneity was observed. Possible sources of heterogeneity were explored through a meta-regression analysis.

Results

Characteristics of the studies

This meta-analysis yielded 279 primary studies after the initial independent review, comprising 278 published studies identified through electronic database searches and 1 published study identified through a manual search. Figure 1 shows the study selection process. A total of 7 records were initially excluded due to duplicate records; 259 records were excluded due to the source not related to the research topic or being conference abstract; and 7 records were excluded because they did the fluid responsiveness test by different dose fluid challenge. Finally, six studies [15, 16, 28–31] fulfilled all the inclusion criteria and were considered for analysis. They are all prospective single center studies, the main characteristics of the eligible studies are shown in Table 1. The quality of the included studies was assessed using QUADAS-2 available in Fig. 2.

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

First author/ Year of publication	Country	patients	Gender (M/f)	Age (year) Mean ± SD	Cases	Tidal Volume (mL/kg)	Index test device	Reference standard measurement	Reference standard Threshold (%)
Monge/ 2012[16]	Spanish	patients with controlled mechanical ventilation and acute circulatory failure	16/21	64 ± 13	37	8.1 ±1.2	Side stream infrared gas analyzer	CO	≥15
Monnet/2013[15]	France	Patients ventilated in the control assisted mode with no inspiratory effort and hemodynamic instability	NA	60 ± 14	40	6.4±0.8	Side stream infrared gas analyzer	CI	≥15
Zang/2013 [28]	China	patients with controlled mechanical ventilation and sepsis shock	22/20	Responder: 56.9±16.6 Nonresponder:57.7±12.3	42	Responder: 7.5±3.6 Nonresponder: 7.7±2.3	Side stream infrared gas analyzer	CI	≥15
Wang/2015 [29]	China	patients with controlled mechanical ventilation and sepsis shock	24/24	Responder: 52.7 ± 29.4 Nonresponder:56.7 ± 26.2	48	NA	Side stream infrared gas analyzer	CI	≥10
Toupin/2016 [30]	Canada	patients receiving mechanical ventilation and undergoing cardiac or ascending aortic surgery	62/28	Responder: 68 ± 10 Nonresponder:65 ± 10	90	6–8	Side stream infrared gas analyzer	CI	≥15
Yao /2016 [31]	China	patients with controlled mechanical ventilation and shock post-cardiac surgery	27/14	Responder: 55.4 ± 9.9 Nonresponder:58.5 ± 9.3	41	8-10	NA	CI	≥15

CI, Cardiac index; CO, cardiac output; SD, standard deviation; TTE, transesophageal echocardiogram. PiCCO, pulse indicator continuous cardiac output; NA, no

Quantitative synthesis

Study data and individual diagnostic estimates are summarized in Table 2. Overall, 298 patients were included in this review, of whom 149 (50%) were fluid responsive. The cutoff values of $\Delta EtCO_2$ varied across studies, ranging from 5–5.8% or absolute increase 2mmHg. The AUROC of individual studies ranged from 0.80 to 0.94. Heterogeneity between studies was assessed with an overall $Q = 4.098$, $I^2 = 51\%$, and $P = 0.064$, indicated substantial heterogeneity. Spearman's correlation coefficient was -0.6 ($p=0.28$), indicating no threshold effect. The pooled sensitivity and specificity for the overall population were 0.79 (95% CI: 0.72–0.85) and 0.90 (95% CI: 0.77–0.96), respectively (Fig. 3). The pooled positive likelihood ratio and negative likelihood ratio were 8.2 (95%CI: 3.2–20.5) and 0.23 (95%CI: 0.16–0.32), respectively. The DOR was 35 (95% CI: 12–107) (Fig. 4). The pooled AUROC was 0.81 (95% CI: 0.77–0.84) (Fig. 5).

Table 2
Summary of results of the studies included in this meta-analysis

First author/ Year of publication	Sample size	Cutoff value (increase in percentage or absolute value)	Subject numbers could be calculated				Sensitivity (%)	Specificity (%)	AUROC (95%CI)
			TP	FP	FN	TN			
Monge/ 2012[16]	37	5%	19	1	2	19	90.5	93.7	0.94 (0.82–0.99)
Monnet/2013[15]	40	5%	15	0	6	15	71	100	0.93 (0.81–0.99)
Zang/2013 [28]	42	5%	21	2	3	21	88	88.2	0.90 (0.775–1.0)
Wang/2015 [29]	48	5%	26	1	8	26	75.8	93.4	0.849 (0.739–0.93)
Toupin/2016 [30]	90	2mmHg	21	19	7	21	75	70	0.80 (0.70–0.90)
Yao /2016 [31]	41	5.8%	16	2	5	16	76.2	90	0.875(0.769–0.981)
AUROC, Area under the receiver operator characteristics curve; CI, confidence interval; FN, false negative; FP, false positive; NA, not available; TN, true negative; TP, true positive.									

Meta-regression analysis results

Meta-regression analyses were performed to investigate the potential causes of heterogeneity using several covariates, as follows: (1)location (China vs. countries other than China), (2)number of patients (≥ 45 vs. <45), (3) reference standard measurement (CO vs. CI), and (4) reference standard device(TEE vs. PiCCO) .The results of the meta-regression analyses (Fig. 6) showed that the significant sources of heterogeneity in sensitivity and specificity were the number of patients.

Publication bias and Sensitivity analysis

The publication bias of the studies was assessed using the Deeks' funnel plot asymmetry test. The slope coefficient of the six studies was associated with a P value of 0.01 (Fig. 7). The aforementioned results indicated significant publication bias. The sensitivity analysis(Fig. 8) showed that excluding Toupin's study[30] negated the publication bias ($p=0.36$). The sensitivity analysis also showed that the pooled DOR ranged from 21 to 140 and the pooled AUC ranged from 0.92 to 0.96 when one study was omitted.

Discussion

The correct evaluation of intravascular volume and proper maintenance of cardiac preload can improve the prognosis of critically ill patients. Static variables could not predict fluid responsiveness[32–35]. However, dynamic indicators of fluid responsiveness, which are based on cardiopulmonary interactions in patients receiving mechanical ventilation, have been shown to be predictive [36–40]. The $\Delta EtCO_2$ has been extensively studied with respect to its value in predicting fluid responsiveness, but the results are conflicting[11–16, 28–31, 41–43]. To the best of our knowledge, this is the first systematic review and meta-analysis to explore the diagnostic accuracy of $\Delta EtCO_2$ in predicting fluid responsiveness during PLR test in patients with mechanical ventilation. The results confirmed that, overall, the $\Delta EtCO_2$ performed well in predicting fluid responsiveness in patients with mechanical ventilation during PLR test, with a pooled AUROC of 0.81 (95% CI: 0.77–0.84), a pooled specificity and sensitivity of 0.90 (95% CI: 0.77–0.96) and 0.79 (95% CI: 0.72–0.85). These findings are clinically relevant because capnography was widely available for critically ill patients, and $\Delta EtCO_2$ values can be obtained immediately in the emergency or critical care setting.

The PLR test provides a dynamic assessment of preload dependence inducing a transient and reversible increase in cardiac preload. This test has been demonstrated to predict fluid responsiveness in many studies over a wide population, including clinical situations in which other parameters of fluid responsiveness have failed, such as patients with cardiac arrhythmias or with spontaneous breathing[44, 45]. However the PLR must be interpreted in conjunction with changes in CO, velocity time integral, aortic blood flow velocity, carotid artery flow time[46],the need for measuring such index usually limits the widespread application of this test to a specific group of patients requiring expensive, burdensome or invasive hemodynamic monitoring systems. EtCO2 can be easily determined with continuous waveform-capnography devices that are generally available in the clinical. In the present study, we showed that fluid responsiveness can be assessed using EtCO2 monitoring and PLR test. This provides a clinically useful way to predict fluid responsiveness using readily available diagnostic tools such as a PLR maneuver and EtCO2 measurement by capnography.

The present systematic review and meta-analysis had some limitations. First, this analysis included only six studies with a relatively small sample size even pooled analysis there are only 298 patients were included in this review. Therefore, the power and precision of the results were limited. Second, the quality assessment showed a high risk of bias in the index test. This bias might have restricted the interpretation of the true diagnostic efficacy of $\Delta EtCO_2$ value in predicting fluid responsiveness. Third, publication bias was observed among studies. We performed a sensitivity analysis and found that the pooled DOR

ranged from 21 to 140 and the pooled AUC ranged from 0.92 to 0.96. This indicates that the results were stable despite the presence of publication bias. Finally, since more detailed individual patient data were not available, a more comprehensive analysis of diagnostic effect could not be conducted.

Conclusions

This was the first meta-analysis to evaluate the diagnostic accuracy of ΔEtCO_2 in predicting fluid responsiveness in patients with mechanical ventilation during PLR test. The study confirmed that the ΔEtCO_2 performed well in predicting fluid responsiveness in patients with mechanical ventilation during PLR test. Further studies with a larger data set and well-designed models are required to confirm the diagnostic accuracy and utility of EtCO_2 in predicting fluid responsiveness in patients with mechanical ventilation during PLR test.

Abbreviations

ΔEtCO_2
Variation of end-tidal carbon dioxide
PLR
Passive leg raising
 EtCO_2
End-tidal carbon dioxide
DOR
Diagnostic odds ratio
CI
Confidence interval
TP
True positive
FP
False positive
TN
True negative
FN
False negative
AUROC
Aarea under the receiver operator characteristic curve
QUADAS-2
Quality Assessment of Diagnostic Accuracy Studies
SROC
Summary receiver operator characteristic
AUC
Area under the SROC curve

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no any conflict of interests.

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Authors' contributions

Haijun Huang and Hua Xu carried out the studies, participated in collecting data, and drafted the manuscript. Chenxia Wu and Qinkang Shen performed the statistical analysis and participated in its design. Yixin Fang helped to draft the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow diagram of identification of studies.

Figure 2

Risk of bias and applicability concerns for the studies included in the meta-analysis. (a) Risk-of-bias graph; (b) Risk-of-bias summary.

Figure 3

Forest plots of the pooled sensitivity and specificity. Each solid square represents an individual study. Error bars represent 95% CI. Diamond indicates the pooled sensitivity and specificity for all of the studies.

Figure 4

Forest plots of the pooled diagnostic odds ratio. Each solid square represents an individual study. Error bars represent 95% CI. Diamond indicates the pooled diagnostic odds ratio for all of the studies.

Figure 5

SROC curve of variation of end-tidal carbon dioxide for predicting fluid responsiveness. Each circle represents individual study estimates. The diamond is the summary point representing the average sensitivity and specificity estimates. The ellipses around this summary point are the 95% confidence region(dashed line) and the 95% prediction region (dotted line). The cutoff value of included studies: (1) Monge/2012[16]:5%; (2) Monnet/2013[15]: 5%; (3) Zang/2013[28]:5%; (4) Wang/2015 [29]: 5%; (5) Toupin/2016 [30]:2mmHg; (6) Yao /2016 [31]: 5.8%.

Univariable Meta-regression & Subgroup Analyses

Figure 6

Graphs for Meta-regression analysis. CI = confidence interval. Meta-regression was performed by refstanddevice (TEE vs. PiCCO),location (China vs. countries other than China),ssize45 (≥45 vs.<45);refstandment (CO vs. CI).

Figure 7

Deeks' funnel plot of publication bias among studies. ESS = effective sample size. Numbers 1 to 6 represent the study arms (Monge/2012, Monnet/2013,Zang/2013,Wang/2015 ,Toupin/2016 ,Yao /2016).

Figure 8

Graphs for sensitivity analysis.

Supplementary Files

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