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Original Article

Role of End-Tidal Carbon Dioxide as a Non-invasive Predictor of Fluid Responsiveness in Mechanically Ventilated Patients with Shock

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Abstract:

Background: *Circulatory shock remains a leading cause of mortality in the intensive care unit, with inadequate tissue perfusion and impaired oxygen delivery as its defining pathophysiological features. Fluid resuscitation is central to early haemodynamic management, as volume expansion increases venous return and augments cardiac output through the Frank–Starling mechanism. However, only approximately half of haemodynamically unstable patients demonstrate a meaningful rise in cardiac output following a fluid bolus, and indiscriminate fluid administration in non-responsive patients carries well-recognised risks including pulmonary oedema, prolonged mechanical ventilation, and increased mortality. Accurate identification of fluid responsiveness prior to fluid administration has therefore become a fundamental component of modern critical care practice. Static haemodynamic parameters such as central venous pressure have been shown by meta-analysis to be unreliable predictors of fluid responsiveness, and dynamic indices such as pulse pressure variation and stroke volume variation, while more accurate, require invasive arterial monitoring and strictly controlled mechanical ventilation. End-tidal carbon dioxide ($EtCO_2$), can be measured continuously by capnography in all mechanically ventilated patients, reflects pulmonary blood flow and hence cardiac output under stable ventilatory conditions, and may offer a simple, non-invasive bedside alternative for predicting fluid responsiveness.*

Methods: *This prospective observational study was conducted in the Intensive Care Unit of Dhaka Medical College Hospital, Dhaka, Bangladesh, between November 2019 and March 2021. One hundred adult patients receiving controlled mechanical ventilation with clinical evidence of shock requiring fluid challenge were enrolled. Patients with significant pulmonary disease, unstable ventilator settings, severe arrhythmias, or contraindications to fluid challenge were excluded. Each patient received a standardized fluid challenge of 500 mL isotonic crystalloid. Cardiac output was measured by transthoracic echocardiography using left ventricular outflow tract velocity-time integral (LVOT-VTI) before and 15 minutes after the fluid challenge. EtCO2 was recorded simultaneously using mainstream capnography. Patients demonstrating a ≥15% increase in cardiac output were classified as fluid responders, consistent with established thresholds in fluid responsiveness research. Pearson correlation and receiver operating characteristic (ROC) curve analysis were used to assess the relationship between EtCO2 change and cardiac output change, and to determine the diagnostic performance of EtCO2.*

Results: *Of 100 patients, 45 (45%) were classified as fluid responders and 55 (55%) as non-responders. Fluid challenge produced significant increases in LVOT-VTI, stroke volume, cardiac output, and EtCO2 across the whole cohort (all $p < 0.001$). Responders demonstrated a significantly greater percentage rise in cardiac output compared with non-responders (20.27 ± 3.90% vs 7.18 ± 3.48%; $p < 0.001$), with a corresponding difference in percentage change in EtCO2 (8.87 ± 2.93% vs 3.58 ± 2.03%; $p < 0.001$). Pearson correlation demonstrated a statistically significant moderate positive correlation between percentage change in cardiac output and percentage change in EtCO2 ($r = +0.678$; $p < 0.001$). ROC curve analysis identified a ≥4.5% increase in EtCO2 as the optimal cut-off for predicting fluid responsiveness, yielding a sensitivity of 97.8%, specificity of 72.7%, positive predictive value (PPV) of 74.6%, negative predictive value (NPV) of 97.6%, and overall diagnostic accuracy of 84%. The area under the ROC curve (AUC) was 0.949 (95% CI: 0.908–0.989; $p < 0.001$), indicating excellent discriminatory performance.*

Conclusion: *A ≥4.5% rise in EtCO2 following a standardised fluid challenge reliably identifies fluid-responsive mechanically ventilated patients with shock, achieving high sensitivity and an excellent AUC of 0.949. The outstanding NPV of 97.6% supports using a flat EtCO2 response as a firm clinical signal to withhold further fluid. EtCO2 monitoring by capnography represents a practical, non-invasive, and readily available bedside tool for guiding fluid therapy, particularly in resource-limited settings where advanced haemodynamic monitoring may be unavailable.*

Keywords: *Cardiac output, Capnography, End-tidal carbon dioxide, Fluid responsiveness, Fluid challenge, Intensive care unit, Shock.*

Introduction

Circulatory shock, regardless of its underlying cause, is defined by inadequate tissue oxygen delivery and demands urgent haemodynamic intervention. Intravenous fluid is usually the first measure employed, with the intention of expanding preload and driving a rise in cardiac output through the Frank–Starling mechanism. This strategy is physiologically sound, but clinical benefit only occurs when

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the left ventricle retains preload reserve and remains on the ascending portion of its Starling curve.[1]

The clinical challenge is that this condition cannot be assumed. Systematic reviews have consistently shown that approximately half of haemodynamically unstable critically ill patients do not respond to a fluid bolus with a meaningful increase in cardiac output.[2] Administering fluid to non-responders raises intravascular and interstitial pressures without improving flow, leading to pulmonary oedema, prolonged mechanical ventilation, abdominal hypertension, and increased mortality.[3] This reality has driven the search for reliable bedside predictors of fluid responsiveness.

Traditional static markers, including central venous pressure and pulmonary artery occlusion pressure, have been shown by repeated meta-analysis to be poor predictors of the cardiac output response to fluid.[3,4] Dynamic indices such as pulse pressure variation (PPV) and stroke volume variation (SVV) offer better discriminatory accuracy,[5] but require a strictly controlled tidal volume, sinus rhythm, and an indwelling arterial line, conditions that are not always satisfied in routine ICU practice.[6]

End-tidal carbon dioxide represents a different approach. Under conditions of stable ventilation and steady metabolic rate, $EtCO_2$ is determined primarily by the rate at which carbon dioxide is transported to the alveoli, which is proportional to pulmonary blood flow and hence to cardiac output.[7,8] When cardiac output rises following a fluid challenge, more CO_2 is delivered per breath and the end-tidal concentration climbs.[9,10] This coupling has been demonstrated in studies using passive leg raising (PLR), but its utility during an actual fluid challenge in a South Asian ICU population has not been well characterised.

We therefore designed this study to determine whether the change in $EtCO_2$ after a standardised crystalloid bolus could reliably predict fluid responsiveness in mechanically ventilated patients with shock, and to identify a clinically applicable diagnostic threshold.

Methodology

Study design and setting: This was a single-centre prospective observational study carried out in the Intensive Care Unit, Department of Anaesthesia, Pain, Palliative and Intensive Care Medicine, Dhaka Medical College Hospital, Dhaka, Bangladesh. Data collection ran from November 2019 to March 2021.

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Study population: Consecutive adult patients (age >18 years) admitted with clinical shock, receiving controlled mechanical ventilation, and having an indication for fluid challenge were considered for inclusion. Shock was defined as a systolic blood pressure below 90 mmHg or mean arterial pressure below 65 mmHg, or a vasopressor requirement, in the presence of clinical signs of tissue hypoperfusion.

Inclusion criteria: (i) age >18 years; (ii) controlled mechanical ventilation; (iii) clinical evidence of shock requiring fluid challenge.

Exclusion criteria: (i) significant primary pulmonary pathology liable to alter the CO_2 transport–$EtCO_2$ relationship independent of cardiac output; (ii) unstable or frequently changing ventilator settings; (iii) severe cardiac arrhythmias; (iv) any contraindication to fluid challenge.

Sample size: A convenience sample of 100 patients who met the inclusion criteria was enrolled over the study period.

Study procedure: With the patient already established on controlled mechanical ventilation and ventilator settings held constant throughout, baseline values of heart rate, blood pressure, LVOT velocity-time integral (LVOT-VTI) by transthoracic echocardiography, and $EtCO_2$ by mainstream capnography were recorded. Stroke volume was calculated as LVOT-VTI multiplied by LVOT cross-sectional area (derived from LVOT diameter measured in the parasternal long-axis view), and cardiac output as stroke volume × heart rate.

Each patient then received a standardised fluid challenge of 500 mL of isotonic crystalloid (0.9% sodium chloride or Ringer's lactate, at the discretion of the treating clinician) infused over approximately 10–15 minutes. No changes were made to ventilator settings, sedation, or vasoactive drug infusion rates during the measurement window. All haemodynamic parameters were re-recorded 15 minutes after completion of the infusion.

Fluid responsiveness was defined as a ≥15% increase in cardiac output from baseline, consistent with the threshold used in contemporary fluid responsiveness research.[2,11]

Statistical analysis: Data were analysed using IBM SPSS Statistics. Continuous variables are presented as mean ± standard deviation (SD). Pre- and post-challenge haemodynamic values within each group were compared using the paired-samples t-test; between-group comparisons used the independent-samples t-test. The association between percentage change in cardiac output and percentage change in $EtCO_2$ was assessed by Pearson correlation coefficient (r). Diagnostic performance was quantified by ROC curve analysis, from which AUC, optimal cut-off (by Youden index), sensitivity, specificity, PPV, NPV, and overall accuracy were derived. A two-tailed p value < 0.05 was considered statistically significant throughout.

Results:

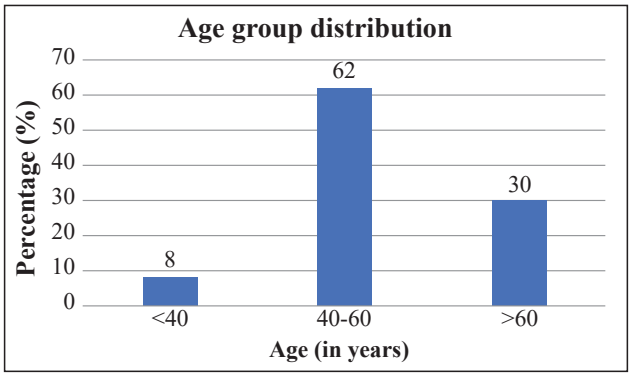


Figure 1: Age distribution of study patients (N=100)

The mean age of the study patients was 53.06 ± 10.75 years (range 31–75) (fig 1). The 40–60 age group predominated, accounting for 62% of patients. Figure 2 showed Gender distribution of study patients. Male patients comprised 61% of the cohort; female patients 39% (male:female ratio ≈ 1.56:1).

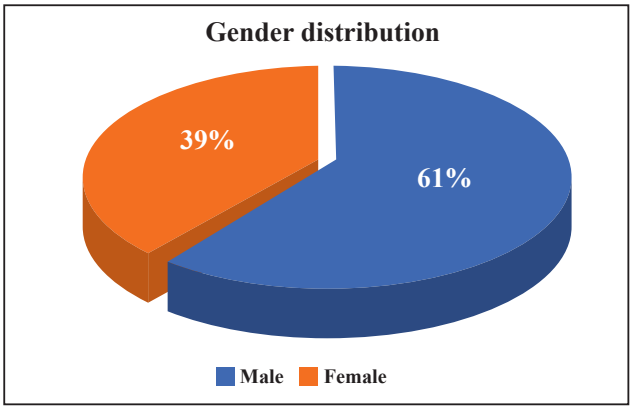


Figure 2: Gender distribution of study patients (N=100)

Table I: Distribution of parameters between before and after fluid challenge (N=100)

Parameters	Before FC (n=100)	After FC (n=100)	pvalue*
Heart rate (bpm)	97.14±8.08	94.38±8.03	<0.001
LVOT-VTI (cm)	17.83±1.37	20.74±2.04	<0.001
Stroke volume (mL)	56.09±7.20	65.27±9.41	<0.001
Cardiac output (L/min)	5.41±0.49	6.11±0.63	<0.001
$EtCO_2$ (mmHg)	34.82±10.76	36.71±10.95	<0.001

Table I shows the comparison of hemodynamic parameters before and after fluid challenge among the patients (n = 100). A significant decrease in mean heart rate was observed after fluid challenge compared with baseline (97.14 ± 8.08 vs 94.38 ± 8.03 bpm). In contrast, significant increases were observed in LVOT-VTI (17.83 ± 1.37 vs 20.74 ± 2.04 cm), stroke volume (56.09 ± 7.20 vs 65.27 ± 9.41 mL), cardiac output (5.41 ± 0.49 vs 6.11 ± 0.63 L/min), and $EtCO_2$ (34.82 ± 10.76 vs 36.71 ± 10.95 mmHg) after fluid challenge. These differences were statistically significant ($p < 0.05$, paired sample t-test).

Table II: Comparison of parameters between before and after fluid challenge according to fluid response (N=100)

Parameters	Before FC (n = 100)	After FC (n = 100)	P_1*
Heart rate			
R (n = 45)	95.76 ± 8.14	92.42 ± 7.96	<0.001
NR (n = 55)	98.27 ± 7.94	95.98 ± 7.8	<0.001
P_2**	0.122	0.026	
LVOT-VTI			
R (n = 45)	17.76 ± 1.4	22.13 ± 1.72	<0.001
NR (n = 55)	17.87 ± 1.35	19.6 ± 1.51	<0.001
P_2**	0.693	<0.001	
Stroke volume			
R (n = 45)	55.76 ± 7.79	69.44 ± 9.63	<0.001
NR (n = 55)	56.35 ± 6.74	61.85 ± 7.76	<0.001
P_2**	0.688	<0.001	
Cardiac output			
R (n = 45)	5.29 ± 0.48	6.36 ± 0.61	<0.001
NR (n = 55)	5.5 ± 0.49	5.89 ± 0.57	<0.001
P_2**	0.051	<0.001	
EtCO2			
R (n = 45)	34.13 ± 10.46	36.97 ± 10.96	<0.001
NR (n = 55)	35.38 ± 11.06	36.5 ± 11.04	<0.001
P_2**	0.566	0.008	

Table II shows the comparison of hemodynamic parameters before and after fluid challenge according to fluid responsiveness among the patients (n = 100). Both responders and non-responders demonstrated significant increases in LVOT-VTI, stroke volume, cardiac output, and $EtCO_2$ after fluid challenge compared with baseline ($p < 0.05$). In responders, LVOT-VTI increased from 17.76 ± 1.40 cm to 22.13 ± 1.72 cm, stroke volume from 55.76 ± 7.79 mL to 69.44 ± 9.63 mL, cardiac output from 5.29 ± 0.48 L/min to 6.36 ± 0.61 L/min, and $EtCO_2$ from 34.13 ± 10.46 mmHg to 36.97 ± 10.96 mmHg. In non-responders, LVOT-VTI increased from 17.87 ± 1.35 cm to 19.60 ± 1.51 cm, stroke volume from 56.35 ± 6.74 mL to 61.85 ± 7.76 mL, cardiac output from 5.50 ± 0.49 L/min to 5.89 ± 0.57 L/min, and $EtCO_2$ from 35.38 ± 11.06 mmHg to 36.50 ± 11.04 mmHg ($p < 0.05$). Baseline values of heart rate, LVOT-VTI, stroke volume, cardiac output, and $EtCO_2$ were similar between responders and non-responders ($p > 0.05$). However, after fluid challenge, significant differences were observed between the two groups, with greater changes in responders ($p < 0.05$).

Table III: Change in cardiac output (CO) and $EtCO_2$ after fluid challenge among responders and non-responders (N=100)

	Responder n=45 (%)	Non-responder n=55 (%)	All n=100 (%)	P value*
CO %change	20.27±3.90	7.18±3.48	13.07±7.49	<0.001
EtCO2 %change	8.87±2.93	3.58±2.03	5.96±3.61	<0.001

Table III shows the comparison of percent change in cardiac output (CO) and $EtCO_2$ after fluid challenge between responders and non-responders. Patients who responded to fluid challenge demonstrated a significantly greater increase in cardiac output compared with non-responders (20.27 ± 3.90% vs 7.18 ± 3.48%, $p < 0.001$). Similarly, the percent change in $EtCO_2$ was significantly higher among responders than non-responders (8.87 ± 2.93% vs 3.58 ± 2.03%, $p < 0.001$). The overall mean percent change was 13.07 ± 7.49% for cardiac output and 5.96 ± 3.61% for $EtCO_2$. Responders demonstrated greater increases in both cardiac output and $EtCO_2$ compared with non-responders.

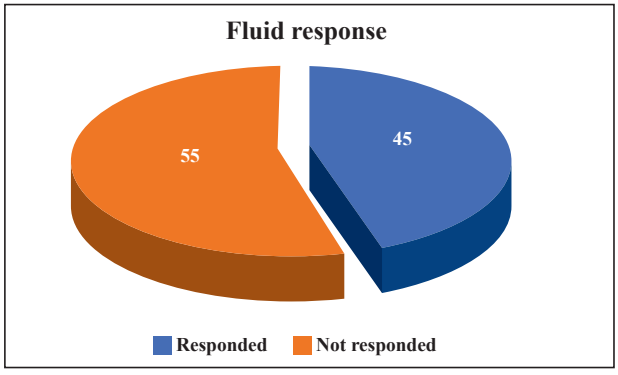


Figure 3: Distribution of study patients according to fluid response (N=100)

Among the 100 patients, forty-five patients (45%) were fluid responders and 55 (55%) were non-responders (fig 3).

Figure 5 shows the receiver operating characteristic (ROC) curve analysis of percent change in $EtCO_2$ for predicting fluid responsiveness after fluid challenge among the patients. The area under the ROC curve was 0.949 (95% CI: 0.908–0.989), indicating excellent predictive accuracy. The optimal cut-off value for predicting fluid responsiveness was a ≥4.5% increase in $EtCO_2$ from baseline. At this cut-off, the sensitivity was 97.8% and the specificity was 72.7%. The result was statistically significant ($p < 0.001$), suggesting that percent change in $EtCO_2$ is a strong predictor of fluid responsiveness in mechanically ventilated patients with shock.

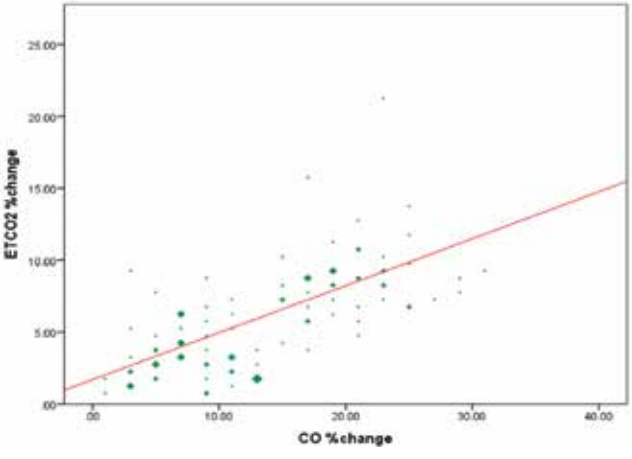
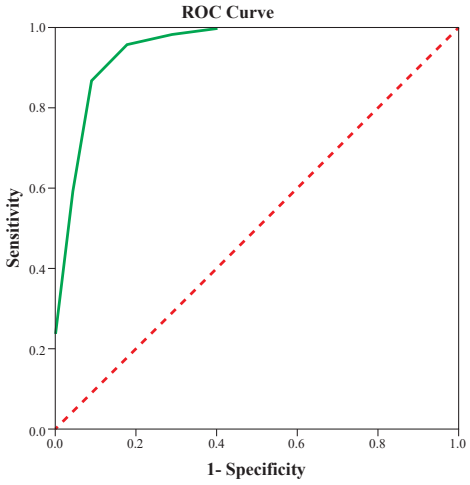


Figure 4: Correlation between percent change of cardiac output (CO) and $EtCO_2$ among patients using scatter plot diagram (N=100). Pearson r = +0.678, p < 0.001.



Diagonal segments are produced by ties.

AUC	Cut-Off value	Sensitivity	Specificity	95% CI Lower	95% CI Upper	P value
0.949	≥4.5	97.8%	72.7%	0.908	0.989	<0.001

Figure 5: Receiver operating characteristic curve showing percent change of EtCO2 in predicting patients who will respond after fluid challenge (N=100)

Table IV: Performance of percent change of $EtCO_2$ in predicting fluid response (N=100)

EtCO2 % change	Fluid responder Yes	No	Total	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
≥4.5	44	15	59					
<4.5	1	40	41	97.8	72.7	74.5	97.56	84
Total	45	55	100					

1Table IV shows the diagnostic performance of percent change in $EtCO_2$ for predicting fluid responsiveness after fluid challenge among the patients. Using a cut-off value of ≥4.5% increase in $EtCO_2$, 44 patients were correctly identified as responders, while 15 were incorrectly classified as responders. Only one responder was misclassified when the change in $EtCO_2$ was < 4.5%, whereas 40 non-responders were correctly identified in this category. The sensitivity and specificity were 97.8% and 72.7%, respectively. The positive predictive value was 74.58%, the negative predictive value was 97.56%, and the overall diagnostic accuracy was 84%. These findings support the strong predictive performance of percent change in $EtCO_2$ for identifying fluid responsiveness in mechanically ventilated patients with shock.

Discussion

The principal finding of this study is that a ≥4.5% rise in EtCO2 following a standardised 500 mL crystalloid challenge predicts fluid responsiveness in mechanically ventilated patients with shock, achieving a sensitivity of 97.8%, specificity of 72.7%, and an area under the ROC curve of 0.949. These results are clinically meaningful for two reasons. First, the AUC of 0.949 places EtCO2-guided assessment among the most accurate non-invasive predictors of fluid

responsiveness reported in the critical care literature.[12,13,14] Second, and perhaps more importantly from a bedside perspective, this diagnostic performance is achieved using a monitor that can be attached to the ventilator circuit of every mechanically ventilated patient, with very minimum equipment, with no procedural intervention, or specialist expertise.

The proportion of fluid responders in this cohort was 45%, which is consistent with the well-established observation that approximately half of all critically ill patients are not fluid responsive at any given point in time.[2,11] This prevalence figure has been reproduced across diverse ICU populations in multiple countries and across different aetiologies of shock.[15,16] Its clinical implication is that the majority of fluid boluses administered without prior assessment of fluid responsiveness are given to patients who will not benefit from them. The consequences of such indiscriminate fluid administration are not trivial. Positive cumulative fluid balance has been independently associated with increased mortality, prolonged mechanical ventilation, impaired renal function, elevated intra-abdominal pressure, and worsening pulmonary oedema.[3,17,18,19] The FENICE study, which surveyed fluid challenge practice across 311 ICUs in 46 countries, found that reassessment of haemodynamic response after fluid administration was performed in fewer than half of cases, highlighting a major gap between evidence and practice.[11] Reliable, low-cost tools to guide fluid decisions are therefore urgently needed.

The search for accurate predictors of fluid responsiveness has evolved considerably over the past two decades. Static haemodynamic parameters, particularly central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP), were for many years the dominant guides to fluid administration in clinical practice. However, a systematic meta-analysis by Marik and Cavallazzi, encompassing 43 studies and over 1800 patients, conclusively demonstrated that CVP has essentially no ability to predict whether a fluid bolus will increase cardiac output.[4] Similar conclusions have been reached for PAOP.[20] The poor performance of these static indices is attributable to their failure to account for ventricular compliance and the nonlinear nature of the Frank–Starling relationship; a given filling pressure may correspond to very different positions on the Starling curve in different patients or even in the same patient at different times.

Dynamic indices, particularly pulse pressure variation (PPV) and stroke volume variation (SVV), represented a major conceptual advance by exploiting the cyclic interaction between positive pressure ventilation and cardiac preload.[5,21] Meta-analyses have confirmed their superior predictive accuracy compared with static parameters, with pooled AUC values typically in the range of 0.84 to 0.94.[5,22] However, their clinical applicability is significantly constrained. They require controlled mechanical ventilation with a tidal volume of at least 8 mL/kg, sinus rhythm, and a closed chest; they are unreliable in patients with right ventricular dysfunction, high respiratory rates, low lung compliance, or elevated intra-abdominal pressure.[23,24,25,26] Furthermore, PPV and SVV require an indwelling arterial catheter, which is not universally available and carries procedural risk.[6] These limitations mean that a substantial proportion of ICU patients cannot be assessed using dynamic arterial waveform analysis, creating a clinical need that $EtCO_2$ monitoring has the potential to fill.

The physiological rationale for using $EtCO_2$ as a surrogate for cardiac output change is well established. Carbon dioxide is produced continuously by cellular metabolism and transported via the venous circulation to the pulmonary capillaries, where it diffuses into the alveoli and is exhaled. Under conditions of stable alveolar ventilation and constant metabolic rate, the concentration of CO_2 at end-expiration is determined primarily by the rate of CO_2 delivery to the lungs, which is directly proportional to pulmonary blood flow and hence to cardiac output.[7,8,27] When cardiac output increases following a fluid bolus, pulmonary blood flow rises, more CO_2 is delivered per breath, and $EtCO_2$ increases. When cardiac output does not increase, the delivery of CO_2 to the lungs remains unchanged and $EtCO_2$ stays flat. This coupling between cardiac output and $EtCO_2$ is the mechanistic basis for the predictive relationship observed in the present study and confirmed by the Pearson correlation coefficient of $r = +0.678$ between percentage change in cardiac output and percentage change in $EtCO_2$.

It is important to note that the $EtCO_2$-cardiac output relationship is only reliable when ventilation is held constant during the measurement window. Any change in respiratory rate, tidal volume, or positive end-expiratory pressure will independently alter $EtCO_2$ through its effect on alveolar ventilation, potentially decoupling it from changes in cardiac output.[27,28] In the present study, ventilator settings were explicitly held constant throughout the fluid challenge protocol, which is a prerequisite that clinicians must observe when applying this method in practice. Similarly, changes in metabolic rate, such as those associated with fever, shivering, or seizure activity, will alter CO_2 production and affect $EtCO_2$ independently of cardiac output.[29] Patients with large physiological dead space, including those with severe pulmonary embolism or advanced ARDS, may show attenuated $EtCO_2$ responses even when cardiac output rises substantially, because much of the additional CO_2 delivered to the lungs is distributed to non-perfused alveoli and does not reach end-tidal gas.[28] This is why we excluded patients with significant primary pulmonary pathology.

Several previous investigators have examined the relationship between EtCO2 and fluid responsiveness, predominantly in the context of passive leg raising rather than an actual fluid challenge. Monnet et al. demonstrated in a cohort of 34 critically ill patients that a ≥5% increase in EtCO2 during PLR predicted a ≥10% rise in pulse contour-derived cardiac output with a sensitivity of 71% and specificity of 100%, outperforming arterial pulse pressure as a predictor.[29] García et al. similarly reported that non-invasive EtCO2 changes during PLR closely tracked changes in cardiac index measured by transthoracic echocardiography, with an AUC of 0.90.[10] Toupin et al. evaluated a simplified PLR protocol and

found that a ≥2.5% increase in EtCO2 identified fluid responders with a sensitivity of 80% and specificity of 85%.[30] Xiao-ting et al. compared EtCO2 during both PLR and a 100 mL mini-fluid challenge, demonstrating predictive utility for PLR but not for the mini-challenge, suggesting that the magnitude of the preload stimulus matters.[13] Jacquet-Lagreze et al. showed that EtCO2 variation after a 500 mL fluid challenge was a reliable predictor of fluid responsiveness, consistent with the findings of the present study.[31] Lakhal et al. reported in a prospective study that change in EtCO2 outperformed all other non-invasive surrogates, including changes in blood pressure and heart rate, as a tracker of cardiac output change during fluid challenge.[12] Young et al. further confirmed that both EtCO2 and volumetric CO2 elimination were reliable predictors of volume responsiveness in haemodynamically unstable patients.[14] Collectively, these studies provide a consistent body of evidence supporting EtCO2 as a valid and practical fluid responsiveness predictor, and the results of the present study add to this evidence with data from a South Asian tertiary ICU population.

Transthoracic echocardiography, the reference standard used in the present study, has itself become an accepted method for assessing fluid responsiveness through measurement of LVOT-VTI response to preload manoeuvres.[1,32] Its advantages include non-invasiveness, absence of radiation, and the ability to simultaneously assess cardiac structure and function. However, TTE is intermittent rather than continuous, requires a trained operator, and is subject to significant inter-observer variability, particularly in LVOT diameter measurement, which has a squared relationship to stroke volume and therefore amplifies small measurement errors.[32] Continuous cardiac output monitoring systems such as transpulmonary thermodilution or oesophageal Doppler provide real-time data but require insertion of dedicated catheters and are not universally available.[33,34] $EtCO_2$ monitoring bridges this gap by providing continuous, real-time data without any procedural requirements, making it well suited to both initial assessment and ongoing monitoring of haemodynamic response to fluid therapy.

The optimal cut-off of ≥4.5% was derived by Youden index from the ROC curve analysis and represents the point that maximises the sum of sensitivity and specificity. The very high sensitivity of 97.8% means that only one of 45 true responders was misclassified by this criterion, a false-negative rate of 2.2%. For a screening test applied at the bedside before committing to further fluid administration, this is an operationally acceptable level of error. The NPV of 97.6% is arguably the most clinically actionable number in this dataset: when EtCO2 rises by less than 4.5% after a fluid bolus, the probability that the patient is a true non-responder exceeds 97%, providing a firm and quantified basis for withholding additional fluid.[35] The specificity of 72.7% and PPV of 74.6% indicate that the test generates false positives in approximately one quarter of cases, meaning that some patients who cross the EtCO2 threshold will not meet the echocardiographic criterion for fluid responsiveness. This modest specificity is consistent with the acknowledged susceptibility of EtCO2 to confounders including metabolic rate, body temperature, dead-space changes, and minor ventilatory fluctuations.[7,28,36] In clinical practice, a positive EtCO2 response should prompt the clinician to consider the full clinical picture rather than mandating automatic further fluid administration.

The definition of fluid responsiveness used in this study, a ≥ 15% rise in cardiac output, is the most widely applied threshold in contemporary fluid responsiveness research and was selected to facilitate comparison with the existing literature.[2,11,37] This cut-off was originally chosen to exceed the typical measurement error of cardiac output monitoring techniques and thereby reduce the risk of classifying measurement noise as a true haemodynamic response.[2] Some investigators have used a ≥10% threshold, which increases the proportion of patients classified as responders but reduces the specificity of the definition.[38] Others have used stroke volume index rather than cardiac output as the criterion variable, which removes the influence of heart rate changes on classification.[37] The 15% cardiac output threshold used here, measured by the validated LVOT-VTI echocardiographic method, represents a practical and reproducible standard. The LVOT-VTI method has been shown to correlate well with thermodilution-derived cardiac output in critically ill patients, and its non-invasive nature makes it particularly suitable for studies in resource-limited settings.[1,32]

The mean age of 53.06 years and the predominance of the 40–60 age group in our cohort is consistent with published demographic data from ICUs in South Asia and other developing regions, where the burden of critical illness is shifting towards middle-aged adults with increasing prevalence of cardiovascular and metabolic comorbidities.[15,16] The male predominance of 61% similarly reflects established patterns of ICU utilisation in this region, influenced by higher rates of cardiovascular disease, occupational hazard exposure, and cultural factors affecting healthcare-seeking behaviour in men.[16] These demographic features may affect the generalisability of our findings to populations with different age structures or gender distributions, and should be considered when applying the derived cut-off value in other settings.

The AUC of 0.949 obtained in the present study is higher than that reported in several previous $EtCO_2$ studies using PLR as the preload stimulus,[9,30] which may partly reflect the larger preload stimulus provided by a 500 mL fluid challenge compared with PLR-induced autotransfusion of approximately 150–300 mL.[37] A larger preload stimulus generates a larger cardiac output response in true responders, widening the separation between the $EtCO_2$ distributions of responders and non-responders and improving diagnostic discrimination. However, this advantage must be weighed against the irreversibility of an actual fluid challenge: unlike PLR, the 500 mL has already been given before the result is known. This reinforces the value of the high NPV in the present study, it provides retrospective reassurance that withholding further fluid after a flat $EtCO_2$ response is safe, but it does not solve the problem of the initial bolus having already been administered to non-responders. Combining

$EtCO_2$ assessment with a reversible preload stimulus such as PLR or an end-expiratory occlusion test before committing to fluid may represent a more conservative and physiologically elegant clinical strategy.[37,38]

From an implementation standpoint, the $EtCO_2$-guided fluid challenge protocol described in this study is straightforward to apply at the bedside. The clinician records the baseline $EtCO_2$ value from the capnograph display, administers 500 mL of isotonic crystalloid over 10–15 minutes while holding ventilator settings constant, and re-reads $EtCO_2$ 15 minutes after completion of the infusion. A rise of 4.5% or more indicates likely fluid responsiveness; a lesser rise suggests non-response and should prompt reassessment of the clinical indication for further fluid. No additional equipment, training, or calculation is required beyond what is already present in any ICU managing ventilated patients. Capnography is a mandatory monitoring standard in mechanically ventilated patients in both high-income and most middle-income country settings,[39-41] meaning that this decision tool is likely to be available to virtually all intensivists who manage ventilated patients with shock.

The clinical relevance of a capnograph-based fluid responsiveness test is perhaps greatest in resource-limited settings, where the advanced monitoring technologies required for dynamic index calculation are often unavailable. In many ICUs across South Asia, Africa, and parts of Latin America, arterial lines are not routinely inserted, and cardiac output monitoring beyond basic echocardiography is rarely accessible.[42] In these environments, fluid management decisions are frequently made on clinical grounds alone, without objective haemodynamic guidance, contributing to both under-resuscitation and fluid overload.[43] A reliable, non-invasive, and equipment-light method for assessing fluid responsiveness has the potential to meaningfully improve the quality of haemodynamic management in these settings, with direct implications for patient outcomes.

Limitations of the Study

Several limitations should be considered when interpreting these findings. First, this was a single-centre study at a tertiary institution in Dhaka; both the patient mix and clinical protocols may differ from those at other centres, and external validity should be confirmed by multicentre data. Second, the sample of 100 patients, while adequate for the primary ROC analysis, is relatively small and may not detect performance differences across subgroups defined by shock aetiology. Third, transthoracic echocardiography is operator-dependent, and inter-observer variability in LVOT-VTI measurement could introduce noise into the cardiac output estimates. Fourth, $EtCO_2$ is influenced by factors other than cardiac output, including dead-space ventilation, metabolic rate, and body temperature, which may reduce its accuracy in patients with significant lung pathology, though we attempted to mitigate this by excluding those with severe pulmonary disease. Finally, our findings are limited to patients receiving controlled mechanical ventilation and cannot be directly extrapolated to spontaneously breathing patients without further study.

Recommendations

Multicentre prospective studies enrolling larger and more heterogeneous cohorts are needed to validate the ≥4.5% EtCO2 threshold across different patient populations, shock aetiologies, and ventilator strategies. Future work should also examine the performance of EtCO2 monitoring combined with passive leg raising, a reversible preload challenge that avoids any net volume load and explore its accuracy in patients with significant right ventricular dysfunction or high dead-space lung disease, where the CO2 transport–EtCO2 coupling may be attenuated. Integration with other low-cost non-invasive indices, such as plethysmographic variability index or inferior vena cava collapsibility, warrants investigation as a means of further improving accuracy in resource-limited settings.

Conclusion:

This study demonstrates that EtCO2 monitoring, which is already in continuous use in every mechanically ventilated patient, can reliably predict fluid responsiveness when assessed as a dynamic change following a standardised crystalloid bolus. A ≥4.5% rise in EtCO2 identifies fluid-responsive patients with 97.8% sensitivity, 72.7% specificity, and an AUC of 0.949. The NPV of 97.6% is particularly clinically useful: when EtCO2 does not rise, further fluid is very unlikely to be beneficial and withholding it appears safe. In settings where invasive or advanced haemodynamic monitoring is unavailable, EtCO2-guided fluid management offers a practical, evidence-based alternative for mechanically ventilated patients with shock.

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References:

1. Cecconi M, Parsons AK, Rhodes A. What is a fluid challenge? Curr Opin Crit Care. 2011;17(3):290–295.
2. Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? JAMA. 2016;316(12):1298–1309.
3. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med. 2011;39(2):259–265.
4. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. Crit Care Med. 2013;41(7):1774–1781.
5. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform-derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009;37(9):2642–2647.
6. Cannesson M, Pestel G, Ricks C, Hoeft A, Perel A. Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists. Crit Care. 2011;15(4):R197.
7. Anderson CT, Breen PH. Carbon dioxide kinetics and capnography during critical care. Crit Care. 2000;4(4):207–215.

8. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. Crit Care. 2010;14(2):220.

9. Monnet X, Bataille A, Magalhaes E, Barrois J, Le Corre M, Gosset C, et al. End-tidal carbon dioxide is better than arterial pressure for predicting volume responsiveness by the passive leg raising test. Intensive Care Med. 2013;39(1):93–100.

10. Monge García MI, Gil Cano A, Gracia Romero M, Monterroso Pintado R, Pérez Madueño V, Díaz Monrové JC. Non-invasive assessment of fluid responsiveness by changes in partial end-tidal CO2 pressure during a passive leg-raising maneuver. Ann Intensive Care. 2012;2:9.

11. Cecconi M, Hofer C, Teboul JL, Pettila V, Wilkman E, Molnar Z, et al. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. Intensive Care Med. 2015;41(9):1529–1537.

12. Lakhal K, Nay MA, Kamel T, Lortat-Jacob B, Ehrmann S, Rozec B, et al. Change in end-tidal carbon dioxide outperforms other surrogates for change in cardiac output during fluid challenge. Br J Anaesth. 2017;118(3):355–362.

13. Xiao-ting W, Hua Z, Da-wei L, Hong-min Z, Huai-wu H, Yun L, et al. Changes in end-tidal CO2 could predict fluid responsiveness in the passive leg raising test but not in the mini-fluid challenge test: a prospective and observational study. J Crit Care. 2015;30(5):1061–1066.

14. Young A, Marik PE, Sibole S, Grooms D, Levitov A. Changes in end-tidal carbon dioxide and volumetric carbon dioxide as predictors of volume responsiveness in hemodynamically unstable patients. J Cardiothorac Vasc Anesth. 2013;27(4):681–684.

15. Boulain T, Boisramé-Helms J, Ehrmann S, Lascarrou JB, Bouglé A, Chiche A, et al. Volume expansion in the first 4 days of shock: a prospective multicentre study in 19 French intensive care units. Intensive Care Med. 2015;41(2):248–256.

16. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006;34(2):344–353.

17. Micek ST, McEvoy C, McKenzie M, Hampton N, Doherty JA, Kollef MH. Fluid balance and cardiac function in septic shock as predictors of hospital mortality. Crit Care. 2013;17(5):R246.

18. Rosenberg AL, Dechert RE, Park PK, Bartlett RH; NIH NHLBI ARDS Network. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. J Intensive Care Med. 2009;24(1):35–46.

19. Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, et al. The importance of fluid management in acute lung injury secondary to septic shock. Chest. 2009;136(1):102–109.

20. Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. Ann Intensive Care. 2011;1(1):1.

21. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest. 2002;121(6):2000–2008.

22. Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. Crit Care. 2014;18(6):650.

23. Díaz F, Erranz B, Donoso A, Salomon T, Cruces P. Influence of tidal volume on pulse pressure variation and stroke volume variation during experimental intra-abdominal hypertension. BMC Anesthesiol. 2015;15:127.

24. Jacques D, Bendjelid K, Duperret S, Colling J, Piriou V, Viale JP. Pulse pressure variation and stroke volume variation during increased intra-abdominal pressure: an experimental study. Crit Care. 2011;15(1):R33.

25. Liu Y, Wei LQ, Li GQ, Yu X, Li GF, Li YM. Pulse pressure variation adjusted by respiratory changes in pleural pressure, rather than by tidal volume, reliably predicts fluid responsiveness in patients with acute respiratory distress syndrome. Crit Care Med. 2016;44(2):342–351.

26. Mahjoub Y, Pila C, Friggeri A, Zogheib E, Lobjoie E, Tinturier F, et al. Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. Crit Care Med. 2009;37(9):2570–2575.

27. Huttmann SE, Windisch W, Storre JH. Techniques for the measurement and monitoring of carbon dioxide in the blood. Ann Am Thorac Soc. 2014;11(4):645–652.

28. McSwain SD, Hamel DS, Smith PB, Gentile MA, Srinivasan S, Meliones JN, et al. End-tidal and arterial carbon dioxide measurements correlate across all levels of physiologic dead space. Respir Care. 2010;55(3):288–293.

29. Tautz TJ, Urwyler A, Antognini JF, Riou B. Case scenario: increased end-tidal carbon dioxide: a diagnostic dilemma. Anesthesiology. 2010;112(2):440–446.

30. Toupin F, Clairoux A, Deschamps A, Lebon JS, Lamarche Y, Lambert J, et al. Assessment of fluid responsiveness with end-tidal carbon dioxide using a simplified passive leg raising maneuver: a prospective observational study. Can J Anaesth. 2016;63(9):1033–1041.

31. Jacquet-Lagrèze M, Baudin F, David JS, Fellahi JL, Huet PB, Lilot M, et al. End-tidal carbon dioxide variation after a 100- and a 500-mL fluid challenge to assess fluid responsiveness. Ann Intensive Care. 2016;6(1):37.

32. Blanco P, Aguiar FM, Blaivas M. Rapid ultrasound in shock (RUSH) velocity-time integral: a proposal to expand the RUSH protocol. J Ultrasound Med. 2015;34(9):1691–1700.

33. Thiele RH, Bartels K, Gan TJ. Cardiac output monitoring: a contemporary assessment and review. Crit Care Med. 2015;43(1):177–185.

34. Lamia B, Kim HK, Severyn DA, Pinsky MR. Cross-comparisons of trending accuracies of continuous cardiac-output measurements: pulse contour analysis, bioreactance, and pulmonary-artery catheter. J Clin Monit Comput. 2018;32(1):33–43.

35. Ray P, Le Manach Y, Riou B, Houle TT. Statistical evaluation of a biomarker. Anesthesiology. 2010;112(4):1023–1040.

36. McDonald MJ, Montgomery VL, Cerrito PB, Parrish CJ, Boland KA, Sullivan JE. Comparison of end-tidal CO2 and PaCO2 in children receiving mechanical ventilation. Pediatr Crit Care Med. 2002;3(3):244–249.

37. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, et al. Passive leg raising predicts fluid responsiveness in the critically ill. Crit Care Med. 2006;34(5):1402–1407.

38. Monnet X, Bleibtreu A, Ferré A, Dres M, Gharbi R, Richard C, et al. Passive leg-raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. Crit Care Med. 2012;40(1):152–157.

39. Cheifetz IM, Myers TR. Respiratory therapies in the critical care setting. Should every mechanically ventilated patient be monitored with capnography from intubation to extubation? Respir Care. 2007;52(4):423–438.

40. Kerslake I, Kelly F. Uses of capnography in the critical care unit. BJA Educ. 2017;17(5):178–183.

41. Ortega R, Connor C, Kim S, Djang R, Patel K. Monitoring ventilation with capnography. N Engl J Med. 2012;367(19):e27.

42. Chawla R, Todi S, editors. ICU Protocols: A Step-wise Approach. 2nd ed. Singapore: Springer; 2020.

43. Marik PE. Handbook of Evidence-Based Critical Care. 2nd ed. New York: Springer; 2021.