Evaluation of end-tidal carbon dioxide gradient as a predictor of volume responsiveness in spontaneously breathing healthy adults

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Abstract

Background: Methods to guide fluid therapy in spontaneously breathing patients are scarce. No studies have reported the accuracy of end-tidal CO₂ (ET-CO₂) to predict volume responsiveness in these patients. We sought to evaluate the ET-CO₂ gradient (ΔET-CO₂) after a passive leg rise (PLR) maneuver to predict volume responsiveness in spontaneously breathing healthy adults.

Methods: We conducted a prospective study in healthy adult human volunteers. A PLR maneuver was performed and cardiac output (CO) was measured by transthoracic echocardiography. ET-CO₂ was measured with non-invasive capnographs. Volume responsiveness was defined as an increase in cardiac output (CO) > 12% at 90 s after PLR.

Results: Of the 50 volunteers, 32% were classified as volume responders. In this group, the left ventricle outflow tract velocity time integral (VTI LVOT) increased from 17.9 ± 3.0 to 20.4 ± 3.4 (p = 0.0004), CO increased from 4.4 ± 1.5 to 5.5 ± 1.6 (p = 0.0), and ET-CO₂ rose from 32 ± 4.84 to 33 ± 5.07 (p = 0.135). Within the entire population, PLR-induced percentage ΔCO was not correlated with percentage ΔET-CO₂ (R² = 0.13; p = 0.36). The area under the receiver operating curve for the ability of ET-CO₂ to discriminate responders from non-responders was of 0.67 ± 0.09 (95% CI 0.498–0.853). A ΔET-CO₂ ≥ 2 mmHg had a sensitivity of 50%, specificity of 97.06%, positive likelihood ratio of 17.00, negative likelihood ratio of 0.51, positive predictive value of 88.9%, and negative predictive value of 80.5% for the prediction of fluid responsiveness.

Conclusions: ΔET-CO₂ after a PLR has limited utility to discriminate responders from non-responders among healthy spontaneously breathing adults.

Keywords: Capnography, Cardiac output, Doppler echocardiography, Blood volume determination, Hemodynamic monitoring

Background

One of the most important goals during the resuscitation of the critically ill patient is to reestablish an adequate oxygen delivery (DO₂) to the tissues. Given the theory that DO₂ depends, among others, on cardiac output (CO), the clinician may consider to give intravenous fluids aiming to increase left ventricular preload and stroke volume (SV). However, it is known that not every patient responds to a volume challenge with...
an increase in CO. Furthermore, fluid administration requires careful monitoring because both, volume deficit and overload, can worsen the prognosis [1, 2].

For this reason, the fundamental challenge is to accurately estimate if the patient will benefit from a volume challenge. Methods to guide fluid therapy in the spontaneously breathing patient are scarce, and many of them require invasive monitoring [3]. This may limit its routine use in patients who present to the emergency department or who are being treated in scenarios that do not have these monitoring tools within reach.

An interesting and non-invasive tool is the evaluation of the aortic flow by transthoracic echocardiography (TTE). Variables such as the change in peak aortic flow velocity and left ventricle outflow tract velocity time integral (VTI LVOT) after a passive leg rise (PLR) maneuver are good predictors of volume responsiveness in critically ill patients (sensitivity 77% and 100% specificity) [4, 5]; however, this echocardiographic measurements require more advanced training, can be difficult to estimate in patients with inadequate acoustic windows, there are important limitations with keeping the same angle between probe and the left outflow tract in both positions, and finally, these measurements take a considerable time to obtain.

The relationship between expired CO₂ (ET-CO₂) and CO has been known for several decades [6, 7]. Since ET-CO₂ is determined mainly by the tissue production of carbon dioxide (CO₂), alveolar ventilation and CO [8], under constant metabolic and ventilatory conditions, acute changes in ET-CO₂ have shown to correlate strongly with changes in CO in experimental [9–11] and clinical [12, 13] scenarios. For this reason, the variation in ET-CO₂ has been used as a method to predict volume responsiveness after a PLR maneuver in the mechanically ventilated patient [14].

To date, there are no published studies evaluating the accuracy of non-invasive ET-CO₂ to predict volume responsiveness in the spontaneously breathing patient. It is well known that healthy individuals can work at various points of the Frank-Starling curve at different times due to small changes in their cardiac contractility and/or effective vascular volume, so a percentage of them can respond to volume at a given moment [15]. Therefore, the objective of this study is to evaluate the performance of the expired CO₂ gradient (ΔET-CO₂) after a PLR maneuver to predict volume responsiveness in spontaneously breathing healthy adults.

**Methods**

**Study population**

We included human volunteers of both sexes, ≥18 years, classified according to the American Society of Anesthesiologists as ASA I or ASA II. This classification (ASA I and II) includes healthy people or with mild systemic diseases without major functional limitations [16]. Volunteers who presented arrhythmias at the time of analysis, lower limb amputation, inadequate cardiac window for VTI LVOT measurement, pregnant women, participants who during the maneuver did not tolerate supine position or leg rise, and finally, patients who refused to participate were excluded.

A non-probability convenience sample was used, estimating a total of at least 50 participants. Volunteers were mainly medical school students, residents, hospital staff, and close contacts of the researchers (family, friends, and colleagues). This study was conducted in the Valle del Lili Foundation Hospital (Cali, Colombia) after approval by...
the Institutional Ethics Committee. All informed consents are duly signed and stored in this department.

Measurements
Participants were contacted individually and required to be fasted, according to the definition of fasting of the American Society of Anesthesiology [17]. In the laboratory, after 2 min of placing the participants on a supine position with head at 45°, baseline hemodynamic variables were recorded (Additional file 1: Table S1). Subsequently, the PLR maneuver was performed, according to the original description of the technique: semi recumbent position, total supine position with leg rise at 45° for 90 s, return to the basal position [18]. The different hemodynamic variables, including capnography, were recorded at 30, 60, 90, 5, 8, and 10 min after the initiation of the maneuver. VTI\textsubscript{LVOT} measurement was taken 90 s, 5 min, and 10 min after the PLR.

For the purpose of this study, the participant who had an increase in CO > 12% after 90 s of PLR was classified as a volume responder. CO was calculated by measuring the left ventricular outflow tract diameter (in the parasternal long axis view), the VTI\textsubscript{LVOT} (in the apical five-chamber view), and the heart rate \( \text{CO} = \pi \left(\frac{D}{2}\right)^2 \times \text{VTI} \times \text{HR} \). All echocardiographic evaluations were performed by experienced sonographers (VZ, LB, CV).

Capnography was measured using Nihon Khoden cap-ONE\textsuperscript{®} TG-920P mainstream CO\textsubscript{2} sensor, attached to a disposable oral and nasal adaptor and placed directly at the point of expiration. The other hemodynamic variables and their source are described in Additional file 1: Table S1.

Data management and statistical analysis
An information quality control to determine missing data and extreme data was carried out. A Shapiro-Wilk test was used to determine the distribution of the numerical variables; these were summarized as mean and standard deviations or median and interquartile ranges, as appropriate. Categorical variables were summarized as proportions.

Differences between responders and non-responders were compared by means of an independent sample \( t \) test, except for age, SpO\textsubscript{2}, VTI\textsubscript{LVOT}, SV, CO, and cardiac index, which were compared by the Mann-Whitney \( U \) test.

The effects of PLR on hemodynamic parameters were assessed using a paired Student’s \( t \) test. The area under the receiver operating curve (ROC) was calculated using the Hanley-McNeil test. ROC curves are presented as area ± SE (95% confidence interval). ET-CO\textsubscript{2}’s capability to track changes in CO during PLR was tested using a concordance analysis through a Pearson correlation coefficient, both for percentage changes and for absolute values at each measuring point.

The best cutoff point was identified and reported in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−). For this purpose, individuals with a decrease in ET-CO\textsubscript{2} after PLR were assumed to have an increase of 0 mmHg. Trend graphs were constructed to evaluate the behavior of the hemodynamic variables over time (30 s–10 min). All statistical analyses were performed using STATA software. A \( p \) value < 0.05 was considered statistically significant.
Results

A total of 50 volunteers were included in the final analysis. The flow of participants through the study is shown in Fig. 1. A large proportion of the population (82%) had no past medical history; only 2 of them were hypertensive, 1 hypothyroid, 1 with sinus bradycardia, 2 with premature ventricular contractions, 2 with mild mitral regurgitation, 1 with a history of vasovagal syncope, and 1 with a history of stage 2 chronic kidney disease. The mean baseline VTI_LVOT was 18.8 ± 2.8 cm, baseline CO was 4.3 ± 1.1 L/min, and baseline ET-CO₂ was 32.0 ± 3.5 mmHg (Table 1).

Of the 50 volunteers, a total of 16 (32%) were classified as volume responders after the PLR. In this group of participants, the VTI_LVOT increased from 17.9 ± 3.01 to 20.4 ± 3.42 (p = 0.0004), CO increased from 4.4 ± 1.45 to 5.5 ± 1.57 (p = 0.00), and ET-CO₂ rose from 32 ± 4.84 to 33 ± 5.07 (p = 0.135) (Table 2). In the group of non-responders, the VTI_LVOT did not show significant changes (from 19.2 ± 2.67 to 19.3 ± 2.33, p = 0.636), nor did the CO (4.3 ± 0.99 to 4.3 ± 0.96, p = 0.474) or the ET-CO₂ (32 ± 2.76 to 32 ± 2.63, p = 0.408) (Table 3). Changes in ET-CO₂, VTI_LVOT, HR, and CO throughout the PLR maneuver among responders and non-responders are shown in Figs. 2 and 3.

Within the entire population, the PLR-induced percentage change in CO was not correlated with changes in ET-CO₂ (R² = 0.13; p = 0.36) (Fig. 4a). There was also no correlation between PLR-induced percentage changes in VTI_LVOT and ET-CO₂ (R² = 0.18; p = 0.21) (Fig. 4b). Correlation between absolute values of CO and ET-CO₂ at each measurement point (basal, 90 s, 5 min, 10 min) were also non-significant (R² = 0.03, p = 0.82; R² = 0.18, p = 0.20; R² = 0.11, p = 0.43; R² = 0.10, p = 0.48, respectively) (Additional file 1: Figure S1).
| Characteristic                                | Total, n = 50 | Non-responders, n = 34 | Responders, n = 16 | p value\# |
|----------------------------------------------|---------------|------------------------|--------------------|-----------|
| Age (years)\[β, Ω\]                          | 27 (23–30)    | 26 (23–29)             | 30 (23–35.5)       | 0.110     |
| Male, n (%)                                  | 26 (52)       | 17 (50)                | 9 (56)             | 0.68      |
| Latin American, n (%)                        | 47 (94)       | 31 (91.2)              | 16 (100)           | 0.542     |
| Afrodescendant, n (%)                        | 3 (6)         | 1 (2.9)                | 0 (0)              |           |
| Weight (kg), mean ± SD                       | 71.48 ± 15.99 | 68.29 ± 15.39          | 78.25 ± 15.56      | 0.039     |
| Height (m), mean ± SD                        | 1.68 ± 0.36   | 1.67 ± 0.11            | 1.71 ± 0.11        | 0.293     |
| Body mass index (kg/m²), mean ± SD          | 24.98 ± 3.60  | 24.18 ± 3.37           | 26.72 ± 3.58       | 0.019     |
| Body surface area (m²), mean ± SD           | 1.82 ± 0.25   | 1.77 ± 0.25            | 1.92 ± 0.24        | 0.058     |
| Heart rate (bpm), mean ± SD                 | 73 ± 12.55    | 73 ± 13.01             | 74 ± 11.92         | 0.853     |
| Systolic blood pressure (mmHg), mean ± SD   | 118 ± 12.74   | 113 ± 11.96*           | 128 ± 8.87         | 0.0001    |
| Diastolic blood pressure (mmHg), mean ± SD  | 73 ± 8.94     | 71 ± 9.21*             | 77 ± 6.83          | 0.011     |
| Mean arterial pressure (mmHg), mean ± SD    | 89 ± 11.53    | 86 ± 10.67**           | 96 ± 10.28         | 0.002     |
| Peripheral capillary oxygen saturation (%)  | 98 (98–99)    | 98 (98–99)             | 97 (96.5–98)       | 0.051     |
| Respiratory rate (rpm), mean ± SD           | 17 ± 4.71     | 17 ± 4.88              | 17 ± 4.5           | 0.845     |
| End-tidal carbon dioxide (mmHg), mean ± SD  | 32 ± 3.50     | 32 ± 2.76              | 32 ± 4.84          | 0.911     |
| End-tidal carbon dioxide (mmHg/respiratory rate)\[β, Ω\] | 1.83 (1.5–2.46) | 1.81 (1.52–2.5) | 1.96 (1.46–2.17) | 0.925 |
| Left ventricle outflow tract VTI (cm\[β, Ω\]) | 18.2 (17.3–21) | 18.9 (17.97–21.1) | 17.9 (16.45–18.2) | 0.075 |
| Left ventricle outflow tract area (cm²), mean ± SD | 3.2 ± 0.68 | 3.1 ± 0.65 | 3.4 ± 0.76 | 0.191 |
| Stroke volume (mL), mean ± SD               | 60.1 ± 16.41  | 60.0 ± 16.07           | 60.5 ± 17.66       | 0.924     |
| Stroke volume index (mL/m²)\[β, Ω\]         | 31.3 (25.34–37.51) | 30.7 (25.2–38.58) | 32.8 (28.41–37.36) | 0.406 |
| Cardiac output (L/min)\[β, Ω\]              | 4.2 (3.53–49.2) | 4.3 (3.54–49.2) | 4.2 (3.31–49.1) | 0.901 |
| Cardiac index (L/min/m²)\[β, Ω\]            | 2.3 (1.89–279) | 2.1 (1.87–2.79) | 2.4 (2.08–2.8) | 0.34 |

SD standard deviation, bpm beats per minute, rpm respirations per minute, VTI velocity time integral
\#Comparison between responders and non-responders
\%Median (interquartile range)
\βMann-Whitney test
*\(n = 32\)
**\(n = 31\)
| Parameter                                    | Basal       | 90 s        | 5 min       | 10 min      | 10 min      |
|----------------------------------------------|-------------|-------------|-------------|-------------|-------------|
| Heart rate (bpm)*                           | 74 ± 11.92  | 80 ± 12.45  | 72 ± 10.89  | 74 ± 12.99  | 0.822       |
| Systolic blood pressure (mmHg)*             | 128 ± 8.87  | 122 ± 12.64 | 122 ± 11.62 | 118 ± 11.44 | 0.013       |
| Diastolic blood pressure (mmHg)*            | 77 ± 6.83   | 72 ± 8.86   | 72 ± 8.94   | 74 ± 9.32   | 0.214       |
| Mean arterial pressure (mmHg)*              | 96 ± 10.28  | 88 ± 11.62  | 90 ± 11.58  | 90 ± 11.47  | 0.072       |
| Peripheral capillary oxygen saturation (%)* | 97 ± 1.2    | 97 ± 1.54   | 97 ± 1.26   | 97 ± 1.48   | 0.138       |
| Respiratory rate (rpm)*                     | 17 ± 4.5    | 16 ± 5.07   | 16 ± 4.31   | 16 ± 4.95   | 0.169       |
| ET-CO2 (mmHg)*                              | 32 ± 4.84   | 33 ± 5.07   | 32 ± 4.52   | 32 ± 4.19   | 0.478       |
| ET-CO2/RR*                                  | 1.98 ± 0.63 | 2.35 ± 1.19 | 2.16 ± 0.75 | 2.25 ± 0.96 | 0.156       |
| Left ventricle outflow tract VTI (cm)*      | 179 ± 3.01  | 20.4 ± 3.42 | 188 ± 3.06  | 186 ± 2.66  | 0.162       |
| Left ventricle outflow tract area (cm²)*    | 34 ± 0.76   | NA          | NA          | NA          | NA          |
| Stroke volume (mL)*                         | 605 ± 1766  | 68.9 ± 19.36| 633 ± 16.95 | 633 ± 18.21 | 0.098       |
| Stroke volume index (mL/m²)*                | 355 ± 1142  | 40.3 ± 12.05| 37.1 ± 11.34| 37.1 ± 11.6 | 0.115       |
| Cardiac output (L/min)*                     | 4.4 ± 1.45  | 5.5 ± 1.57  | 4.6 ± 1.43  | 4.6 ± 1.32  | 0.259       |
| Cardiac index (L/min/m²)*                   | 26 ± 0.88   | 3.2 ± 0.94  | 2.7 ± 0.89  | 2.7 ± 0.83  | 0.281       |

SD: standard deviation, bpm: beats per minute, rpm: respirations per minute, ET-CO2: end-tidal carbon dioxide, RR: respiratory rate, VTI: velocity time integral, NA: does not apply
#Comparison of 90 s against baseline parameters
*Comparison of 5 min against baseline parameters
\(^{\dagger}\)Comparison of 10 min against baseline parameters
*Paired t-test
| Parameter                                      | Basal (n=32) | 90 s (n=32) | 5 min (n=32) | 10 min (n=32) | p value<sup>5</sup> | 5 min (n=32) | 10 min (n=32) | p value<sup>5</sup> |
|-----------------------------------------------|--------------|-------------|--------------|---------------|---------------------|--------------|---------------|---------------------|
| Heart rate (bpm)*                             | 73 ± 13.01   | 73 ± 13.65  | 70 ± 12.23   | 71 ± 13.74    | 0.007               |              |               |                     |
| Systolic blood pressure (mmHg)*, n = 32       | 113 ± 11.96  | 112 ± 12.03 | 111 ± 11.39  | 110 ± 10.90   | 0.091               |              |               |                     |
| Diastolic blood pressure (mmHg)*, n = 32      | 71 ± 9.21    | 67 ± 9.56   | 67 ± 8.08    | 67 ± 8.37     | 0.008               |              |               |                     |
| Mean arterial pressure (mmHg)*, n = 31         | 86 ± 10.67   | 83 ± 10.41  | 83 ± 9.09    | 81 ± 9.75     | 0.025               |              |               |                     |
| Peripheral capillary oxygen saturation (%)*   | 98 ± 1.21    | 98 ± 1.32   | 98 ± 1.85    | 98 ± 1.64     | 0.231               |              |               |                     |
| Respiratory rate (bpm)*                       | 17 ± 4.88    | 18 ± 5.98   | 17 ± 4.4     | 16 ± 4.31     | 0.484               |              |               |                     |
| ET-CO2 (mmHg)*                                | 32 ± 2.76    | 32 ± 2.63   | 32 ± 3       | 31 ± 3        | 0.019               |              |               |                     |
| ET-CO2/RR*                                    | 2.08 ± 0.82  | 2.03 ± 1.11 | 2.02 ± 0.77  | 2.11 ± 0.85   | 0.892               |              |               |                     |
| Left ventricle outflow tract VTI (cm)*        | 192 ± 2.67   | 193 ± 2.33  | 18.8 ± 2.58  | 18.9 ± 2.67   | 0.239               |              |               |                     |
| Left ventricle outflow tract area (cm<sup>2</sup>)* | 3.1 ± 0.65  | NA          | NA           | NA            | 0.155               |              |               |                     |
| Stroke volume (mL)*                           | 600 ± 16.07  | 606 ± 16.33 | 586 ± 15.73  | 58.9 ± 15.6   | 0.195               |              |               |                     |
| Stroke volume index (mL/m<sup>2</sup>)*       | 3.26 ± 10.17 | 33.1 ± 10.22| 32.1 ± 10.36 | 32.2 ± 9.88   | 0.371               |              |               |                     |
| Cardiac output (L/min)*                       | 4.3 ± 0.99   | 4.3 ± 0.96  | 40 ± 0.89    | 40 ± 0.98     | 0.014               |              |               |                     |
| Cardiac index (L/min/m<sup>2</sup>)*          | 2.3 ± 0.6    | 2.3 ± 0.58  | 2.2 ± 0.59   | 2.2 ± 0.6     | 0.036               |              |               |                     |

<sup>SD</sup> standard deviation, <sup>bpm</sup> beats per minute, <sup>rpm</sup> respirations per minute, <sup>ET-CO2</sup> end-tidal carbon dioxide, <sup>RR</sup> respiratory rate, <sup>VTI</sup> velocity time integral, NA does not apply
<sup>a</sup>Comparison of 90 s against baseline parameters
<sup>b</sup>Comparison of 5 min against baseline parameters
<sup>c</sup>Comparison of 10 min against baseline parameters
<sup>d</sup>Comparison of 10 min against baseline parameters
<sup>e</sup>Paired t test
The area under the ROC curve for $\Delta$ET-CO$_2$ was of 0.67 ± 0.09 (95% CI 0.498–0.853) (Fig. 5). A $\Delta$ET-CO$_2$ $\geq$ 2 mmHg had a sensitivity of 50%, specificity of 97.06%, LR + of 17.00, and LR− of 0.51 for the prediction of fluid responsiveness (Table 4). The PPV for this same cutoff point was 88.9% and the NPV was 80.5%. The performance for the other cutoff points is shown in Table 4. The performance analysis taking $\Delta$VTI$_{LVOT}$ as a gold standard is included in Additional file 1: Table S2.

In order not to ignore the probable effect of the heart rate in the determination of the CO, trend curves throughout the PLR maneuver were constructed. In the group of responders, both the VTI$_{LVOT}$ and the HR (baseline 74 ± 11.92, 90 s 80 ± 12.45, $p$ = 0.0033) significantly increased from baseline to 90 s. In the group of non-responders, although there was a slight but not significant rise in VTI$_{LVOT}$, HR remained unchanged (baseline 73 ± 13.01, 90 s 73 ± 13.65, $p$ = 0.848) (Table 3).

**Discussion**

According to the results of this study, the PLR-induced change in CO was not correlated with changes in ET-CO$_2$ ($R^2$ = 0.13; $p$ = 0.36) in spontaneously breathing healthy adults. The area under the ROC curve for $\Delta$ET-CO$_2$ showed little utility of this measurement to discriminate responders from non-responders (0.67 ± 0.09; 95% CI 0.498–0.853) (Fig. 5). Interestingly, a $\Delta$ET-CO$_2$ $\geq$ 2 mmHg had a specificity of 97.06%, LR+ of 17.00, PPV of 88.9%, and NPV of 80.5% for the prediction of fluid responsiveness (Table 4). This is consistent with the findings of Monge et al., who found that in mechanically ventilated patients with acute circulatory failure, an absolute increase in ET-CO$_2$ $\geq$ 2 mmHg during PLR was associated with a positive response to fluid administration in all cases [14].
To our knowledge, there is no study that has attempted to evaluate \( \Delta \text{ET-CO}_2 \) post-PLR to predict volume responsiveness in individuals under spontaneous breathing. In this subgroup, one of the most studied tests for this purpose is the ultrasonographic measurement of CO and its surrogates after a PLR maneuver. PLR provides a rapid and reversible ‘self’ volume challenge [18]. A meta-analysis published in 2010 found that this maneuver has a grouped sensitivity and specificity of 89.4 and 91.4%, respectively. The threshold for the prediction of volume responsiveness varied within studies between 8 and 15% [19]. However, although the heterogeneity according to the meta-analysis was not significant, studies included patients both ventilated and in spontaneous breathing. In addition, some studies used CO measurements as the gold standards, others used cardiac index, SV, or VTILVOT. Some used TTE, others tranesophageal echocardiography (TEE), minimally invasive CO monitoring through PiCCO® or Vigileo/FloTrac® systems, or invasive CO monitoring through pulmonary artery catheter.

Two studies performed on patients in spontaneous breathing and with echocardiographic measurements of CO should be highlighted. The first, published by Maizel et al., found that a change in CO > 5% after a PLR discriminates responders from non-responders with a sensitivity of 94%, specificity of 83%, PPV of 83%, and NPV of 94%. In this same study, a change in SV > 8% discriminated responders with a sensitivity of 88%, specificity of 83%, PPV of 82%, and NPV of 88% [5]. The second study published by Lamia et al. found that a change in the VTILVOT > 12.5% discriminated responders with a sensitivity of 70% and specificity of 100% [4].

When evaluating stroke volume, Biais et al. found that a change in SV > 13% measured by TTE after PLR had a sensitivity of 100% and specificity of 80% to
predict volume responsiveness [20]. On their side, Préau et al. found that in patients with severe pancreatitis or sepsis, a change in SV > 10% had a sensitivity, specificity, PPV, and NPV of 86, 90, 86, and 90%, respectively [21].

Fig. 4 Correlation between PLR-induced changes in ET-CO₂ and a CO and b VTI LVOT. ET-CO₂, end-tidal carbon dioxide; VTI LVOT, left ventricle outflow tract velocity time integral; CO, cardiac output

R² = 0.13; p = 0.36

R² = 0.17; p = 0.21
However, the acoustic window for optimal aortic flow Doppler alignment in critically ill patients and the technical difficulty to keep the same probe angle during the PLR maneuver make this measurement not always feasible in the daily clinical practice.

The results of this study suggest that ΔET-CO₂ after a PLR maneuver lack utility to predict volume responsiveness among healthy adult individuals. However, some considerations must be taken into account. First, although echocardiography is validated for CO determination, with VTI LVOT as the variable with less interobserver variability, it is not free from limitations due to angulation and beam alignment difficulties [22]. This may explain why ET-CO₂ has shown better correlation with invasive measurements [12, 13] rather than ultrasonographic estimations of CO [14].

Second, there was a concern about the possible influence of heart rate when defining an individual as volume responder, so trend curves throughout the PLR maneuver were constructed. Within responders, both the VTI LVOT (baseline 17.9 ± 3.01, 90 s 20.4 ± 3.42, \( p = 0.0004 \)) and the heart rate (basal 74 ± 11.92, 90 s 80 ± 12.45; \( p = 0.003 \)) had a statistically significant increase from baseline to 90 s. In contrast, within non-responders, although there was a slight but not significant increase in VTI LVOT (basal 19.2 ± 2.67,

![Fig. 5](image)

**Table 4** Performance of ΔET-CO₂ post-PLR against ΔCO ≥ 12% for the prediction of volume responsiveness

| Cut-point (mmHg) | Sensitivity (%) | Specificity (%) | Correctly classified (%) | LR⁺ | LR⁻ |
|-----------------|----------------|-----------------|--------------------------|-----|-----|
| ≥ 0             | 100.00         | 0.00            | 32                       | 1.00| NA  |
| ≥ 1             | 56.25          | 58.82           | 58                       | 1.37| 0.74|
| ≥ 2             | 50.00          | 97.06           | 82                       | 17.00| 0.51|
| ≥ 3             | 37.5           | 100.00          | 80                       | NA  | 0.62|
| ≥ 6             | 62.5           | 100.00          | 70                       | NA  | 0.94|
| > 6             | 0.00           | 100.00          | 68                       | NA  | 1.00|

LR likelihood ratio, NA does not apply
90 s 19.3 ± 2.33, \( p = 0.636 \), HR remained unchanged (baseline 73 ± 13.01, 90 s 73 ± 13.65, \( p = 0.848 \)) (Table 3).

Finally, despite the fact that the ΔET-CO2 had poor correlation with CO, and the ROC suggested limited utility to discriminate responders from non-responders, interestingly a ΔET-CO2 ≥ 2 mmHg had a specificity of 97.06%, LR+ of 17.00, PPV of 88.9%, and NPV of 80.5% for the prediction of fluid responsiveness (Table 4). This may be due to the characteristics of the study population. It is known that healthy adults can respond with an increase in CO or SV after a “hed-down tilt” maneuver [23]. However, Parker et al. described how in the healthy human, at rest and in supine decubitus, the ventricular function curve is at its maximum with an end diastolic pressure of the left ventricle of approximately 10 mmHg. Below this point, there is a strong direct relationship between filling pressure and cardiac performance, while with higher filling pressures a plateau occurs. Therefore, in the supine position, the normal heart is usually not in the steep part of the ventricular function curve, but is in a unique position in which the cardiac output is possibly controlled by factors other than the filling pressures of the heart [24]. Probably, in acute and critical illness, there is greater variability in the individual positions among the ventricular function curve, and there is therefore greater probability to induce a change in CO after a volume challenge, as has already been described in mechanically ventilated patients with acute circulatory failure [14].

This study has some limitations that have to be accounted. First, because of the inherent limitations of echocardiography due to angulation and beam alignment difficulties [22], ET-CO2 has shown better correlation with invasive measurements [12, 13] rather than ultrasonographic estimations of CO [14]. However, recent studies have demonstrated a significant correlation \((r = 0.95; p < 0.0001)\) between TTE and pulmonary artery catheter (PAC) CO measurement, with a median bias of 0.2 L/min, limits of agreement between −1.3 and 1.8 L/min and a precision of 9% for TTE (vs 8% for PAC) [25]. This way we felt confident to avoid an invasive method for the estimation CO in healthy volunteers.

Second, during spontaneous breathing, measurement of ET-CO2 by direct or lateral capnography is limited by the inevitable air leak from the system, and the technique has low sensitivity to detect hypoventilation in sedated patients [26]. However, in patients who are not under the effects of sedation, direct or lateral capnographs coupled to nasal cannula have good diagnostic performance [27–29], which may even be comparable with capnography in patients on mechanical ventilation [30].

Third, for the echocardiographic estimation of CO there is an important difficulty when trying to keep the same angle between the probe and the LVOT in both semi recumbent and leg raised positions. For the purpose of this study, we did not opt for the mathematical correction of the effects of angulation, but tried to optimize the angulation of the transducer to make it as parallel to the flow as possible. Finally, the technical difficulties of performing these measurements in individuals with inadequate acoustic windows cannot be ignored, although it was not necessary to exclude any participant for this reason. All ultrasonographic measurements were made by experienced sonographers (VZ, LB, CV).

**Conclusions**

According to the results of this study, the performance of ΔET-CO2 for the prediction of volume responsiveness in spontaneously breathing healthy adults revealed a sensitivity
of 50%, specificity of 97.06%, LR + of 17.00, LR− of 0.51, PPV of 88.9%, and NPV of 80.5% for a ΔET-CO2 ≥ 2 mmHg. The area under the ROC curve for ΔET-CO2 was of 0.67 ± 0.09 (95% CI 0.48–0.85), suggesting limited utility of this measurement to discriminate responders from non-responders. PLR-induced changes in CO were not correlated with changes in ET-CO2 (R² = 0.13; p = 0.36) in spontaneously breathing healthy adults.

Additional file

**Additional file 1:** Table S1. Hemodynamic variables and source of origin. Table S2. Performance of ΔET-CO2 post-PLR against ΔVTI ≥ 12.5% for the prediction of volume responsiveness. Figure S1. Correlation between absolute values of ET-CO2 and CO at (A) baseline (B) 90 s (C) 5 min and (D) 10 min after a PLR maneuver. (DOCX 177 kb)

**Abbreviations**

CO: Cardiac output; CVP: Central venous pressure; ET-CO2: End-tidal CO2; IVC: Inferior vena cava; PLR: Passive leg rise; SV: Stroke volume; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography; VTI LVOT: Left ventricle outflow tract velocity time integral; ΔET-CO2: End-tidal CO2 gradient

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**Availability of data and materials**

The datasets supporting the conclusions of this article are included within the article and its additional files.

**Authors’ contributions**

MCA conceived of the study and participated in the design, created the database, contributed to the data acquisition, and wrote the paper. This author is the guarantor of the paper and takes responsibility for the integrity of the work as a whole. MCA, VZ, and LAB participated in the study design. VZ and LAB performed echocardiographic assessments. All authors helped in the drafting of the work or revised it critically for important intellectual content, read and approved the final manuscript. Finally, all the authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Ethics approval and consent to participate**

This research is in line with the international recommendations on human research, the Nuremberg code, the Helsinki agreement, and the CIOM guidelines. This study was approved by the Institutional Ethics Committee of the Fundación Valle del Lili Hospital (approval letter no. 611-2017). The study protocol is registered in this department under the number 1184.

**Consent for publication**

All informed consents are duly signed and stored in the Institutional Ethics Committee of the Fundación Valle del Lili Hospital (Cali–Colombia).

**Competing interests**

The authors declare that they have no competing interests.

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