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Association Between End-Tidal Carbon Dioxide Pressure and Cardiac Output During Fluid Expansion in Operative Patients Depend on the Change of Oxygen Extraction

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Abstract: In a model of hemorrhagic shock, end-tidal carbon dioxide tension ($EtCO_2$) has been shown to reflect the dependence of oxygen delivery (DO_2) and oxygen consumption (VO_2) at the onset of shock. The objectives of the present study were to determine whether variations in $EtCO_2$ during volume expansion (VE) are correlated with changes in oxygen extraction (O_2ER) and whether $EtCO_2$ has predictive value in this respect.

All patients undergoing cardiac surgery admitted to intensive care unit in whom the physician decided to perform VE were included. $EtCO_2$, cardiac output (CO), blood gas levels, and mean arterial pressure (MAP) were measured before and after VE with 500 mL of lactated Ringer solution. DO_2, VO_2, and O_2ER were calculated from the central arterial and venous blood gas parameters. $EtCO_2$ responders were defined as patients with more than a 4% increase in $EtCO_2$ after VE. A receiver-operating characteristic curve was established for $EtCO_2$, with a view to predicting a variation of more than 10% in O_2ER.

Twenty-two (43%) of the 51 included patients were $EtCO_2$ responders. In $EtCO_2$ nonresponders, VE increased MAP and CO. In $EtCO_2$ responders, VE increased MAP, CO, $EtCO_2$, and decreased O_2ER. Changes in $EtCO_2$ were correlated with changes in CO and O_2ER during VE ($P < 0.05$). The variation of $EtCO_2$ during VE predicted a decrease of over 10% in O_2ER (area under the curve [95% confidence interval]: 0.88 [0.77–0.96]; $P < 0.0001$).

During VE, an increase in $EtCO_2$ did not systematically reflect an increase in CO. Only patients with a high O_2ER (i.e., low $ScvO_2$ values) display an increase in $EtCO_2$. $EtCO_2$ changes during fluid challenge predict changes in O_2ER.

(*Medicine* 95(14):e3287)

Abbreviations: $CaCO_2$ = arterial CO_2 contents, CaO_2 = arterial O_2 contents, CO = cardiac output, $CvCO_2$ = venous CO_2 contents, CvO_2 = venous O_2 contents, CVP = central venous pressure, DO_2 = oxygen delivery, HR = heart rate, ICU = intensive care unit, MAP = mean arterial pressure, O_2ER = oxygen extraction, PaO_2 = arterial oxygen pressure, PLR = passive leg raising, PvO_2 = venous oxygen pressure, SaO_2 = arterial oxygen saturation, SV = stroke volume, SvO_2 = central venous oxygen saturation, VCO_2 = carbon dioxide production, VO_2 = oxygen consumption.

INTRODUCTION

The objective of volume-based hemodynamic resuscitation is to raise cardiac output (CO) and increase or restore the delivery of oxygen (DO_2) required to meet the demands of oxygen consumption (VO_2).[1] If DO_2 drops below a critical threshold, oxygen extraction (O_2ER) cannot increase in proportion to demand, and VO_2 becomes dependent on DO_2. Before critical O_2ER values arise, DO_2 can decrease independently of VO_2 (because DO_2 exceeds VO_2) and O_2ER will increase with demand (as demonstrated by a progressive fall in central venous saturation [$ScvO_2$]).[2] When O_2ER cannot rise any further, VO_2 decreases and the body's metabolism becomes partially anaerobic (with a resulting increase in blood lactate levels).[3] In many pathological situations, VO_2 remains constant over a wide range of DO_2 values as a result of adjustments in tissue oxygen uptake.[4] $ScvO_2$ is a clinically meaningful measure of tissue oxygenation,[5] since it assesses the adequacy of DO_2 with regard to VO_2.[6] Several studies have shown that $ScvO_2$-based hemodynamic resuscitation is associated with lower morbidity and mortality rates during anesthesia and intensive care.[7,8] Exhaled CO_2 (end-tidal carbon dioxide tension, $EtCO_2$) is also monitored in patients in the intensive care unit (ICU) or during anesthesia.[9] Over short periods (and assuming a constant metabolic state), there is a qualitative relationship between $EtCO_2$ and CO.[10,11] Thus, $EtCO_2$ can be used as a noninvasive, continuous measure of CO during several clinical situations with low-flow states.[10–13] These results have not been confirmed in patients scheduled for surgery, in whom CO increased upon volume expansion (VE).[14] One possible explanation is that patients scheduled for surgery and patients in the ICU differ in terms of systemic oxygen supply dependency. Most of the literature studies were performed in low-flow states, in which patients have been on a dependence phase between DO_2 and VO_2. This is probably not the case for most patients in the operating theatre. Based on a model of hemorrhagic shock in dogs, Guzman et al[12] demonstrated that $EtCO_2$ can reflect the dependence of DO_2 and VO_2 at the onset of shock and during hemodynamic resuscitation. Thereafter, Dubin et al[13] confirmed the relationship between $EtCO_2$, DO_2, and VO_2. Lastly, $EtCO_2$ may be a noninvasive indicator of O_2ER (and its surrogate $ScVO_2$). Hence, the

Editor: Tomasz Czarnik.
Received: December 10, 2015; revised: February 3, 2016; accepted: March 13, 2016.
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Acquisition of data: P-GG, MG, AHH, MT, PH, SB, KK, EB, HD, EL; analysis and interpretation: P-GG, HD, EL; and drafting the manuscript for important intellectual content: P-GG, MG, EL.
This study has been approved by the IRB of Amiens University Hospital.
The authors have no funding and conflicts of interest to disclose.
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ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003287

primary objective of the present study was to confirm that variations in $EtCO_2$ during VE are correlated with changes in O_2ER. We also evaluated the ability of variations in $EtCO_2$ to predict a decrease in O_2ER during VE.

METHODS

Ethics

The study's objectives and procedures were approved by the local independent ethics committee. Ethical approval for this study (Ethical Committee No. RNI2014-15) was provided by the Comité de Protection des Personnes Nord-Ouest II CHU—Place V. Pauchet, 80054 AMIENS Cedex 1 (Chairperson Bourgueil Thierry) on June 26, 2014. All patients received written information on the study and gave their verbal consent to participation prior to surgery. The present manuscript was drafted in compliance with the STROBE checklist for cohort studies.[15]

Patients

This prospective, observational study started on June 30, 2014 at Amiens University Hospital's cardio vascular and thoracic ICU over a 6-month period. The inclusion criteria were any major patient over 18 years, ventilated with controlled positive ventilation, for whom the physician decided to do a VE within hours of admission to the ICU. The indications for VE were arterial hypotension (systolic arterial pressure [SAP] lower than 90 mm Hg and/or mean arterial pressure [MAP] lower than 65 mm Hg), oliguria (urine output lower than 0.5 mL/kg per h over 1 h), clinical signs of hypoperfusion (skin mottling, capillary refill time over 2 s), and arterial hyperlactatemia (arterial lactate over 2 mmol/L). The noninclusion criteria were permanent arrhythmia, chronic obstructive pulmonary disease, and acute lung injury. The exclusion criteria were spontaneous ventilation, poor echogenicity, and arrhythmia.

Hemodynamic Parameters

An internal jugular vein central venous catheter and an arterial catheter were placed in all patients. Central venous pressure (CVP) and blood pressure were measured with a transducer zeroed at the mid-axillary line. Transthoracic echocardiography (Cx50, Philips Medical System, Suresnes, France) was performed by a physician who was blinded to the study outcomes. The left ventricular ejection fraction was measured using Simpson biplane method with a 4-chamber view. The diameter of the left ventricular outflow tract (LVOT) was measured on a long-axis parasternal view upon patient inclusion. Aortic area (SAo, in cm^2) was calculated as $\pi \times LVOT^2/4$. The aortic velocity-time integral (VTIAo) was measured with pulsed Doppler and a 5-chamber apical view. Stroke volume (SV) (mL) was calculated as VTIAo × SAo. CO (in L/min) was calculated as SV × heart rate (HR). Mean echocardiographic parameters were calculated from 5 measurements (regardless of the respiratory cycle) and analyzed retrospectively. The intra and inter reproducibility of VTIAo measurements was tested prior to the study. Reproducibility values were $4.4 \pm 3.9\%$ and $4.4 \pm 3.2\%$, respectively.

Oxygenation Parameters and $EtCO_2$

We recorded the ventilator settings (tidal volume, plateau pressure, and end-expiratory pressure) at baseline. Exhaled CO_2 was continuously measured at the tip of the endotracheal tube using a CO_2 cuvette with an integrated sensor (Drager, Luebeck, Germany). All parameters were measured on arterial and central venous blood gases. Arterial and venous blood gas levels, the lactate level, the blood hemoglobin concentration, and oxyhemoglobin saturation were assayed using an automated analyzer (ABL800 FLEX, Radiometer, Bronshoj, Denmark). Arterial oxygen content (CaO_2) and venous oxygen content (CvO_2) were calculated as follows: $CaO_2 = 1.34 \times Hb \times SaO_2 + 0.003 \times PaO_2$; $CvO_2 = 1.34 \times Hb \times ScvO_2 + 0.003 \times PvO_2$, where Hb is the hemoglobin concentration (in g/dL), PaO_2 is the arterial oxygen pressure (in mm Hg), SaO_2 is the arterial oxygen saturation (in %), PvO_2 is the venous oxygen pressure (mm Hg), $ScvO_2$ is the central venous oxygen saturation (in %), and 0.003 the solubility coefficient of oxygen. PCO_2 gap was calculated as follow: $PCO_2\ gap = PcvCO_2 - PaCO_2$ (mm Hg).

DO_2 and VO_2 were calculated from arterial and central venous blood gases as follows: DO_2 (mL/min per kg) = ($CaO_2 \times 10 \times CO$)/weight; VO_2 (mL/min per kg) = the arteriovenous difference in oxygen content ($[C(a-v)O_2] \times CO \times 10$)/weight. O_2ER was defined as VO_2/DO_2 ratio. Arterial and venous CO_2 contents ($CaCO_2$, $CvCO_2$) were calculated according to Douglas Formula.[16] The alveolar dead space (Vd/Vt) was estimated from $EtCO_2$ and $PaCO_2$ as $(PaCO_2 - EtCO_2)/PaCO_2$.[17]

Study Procedures

The following clinical parameters were recorded: age, gender, weight, and main diagnosis. First, a passive leg-raising (PLR) test was performed in order to evaluate the effects on SV, and assess preload status. After an equilibration period, baseline measurements of HR, SAP, MAP, diastolic arterial pressure (DAP), CVP, SV, CO, $EtCO_2$, and arterial/venous blood gas levels were obtained. In the present study, VE always consisted in infusing 500 mL of lactated Ringer solution over 10 min; 10 min after VE, a second set of measurements (SAP, MAP, DAP, HR, CVP, SV, CO, $EtCO_2$, and arterial/venous blood gas levels) was recorded. All patients had been sedated via the continuous infusion of propofol and were fully accustomed to mechanical ventilation. All patients underwent mechanical ventilation in volume-controlled mode with a tidal volume set to 7 to 9 mL/kg of ideal body weight, and a positive end-expiratory pressure of 5 to 8 cm H_2O. Ventilator settings (oxygen inspired fraction, tidal volume, respiratory rate, and end positive pressure) and norepinephrine dosage were not modified during the study period.

Statistical Analysis

We calculated that a sample of 50 patients would be sufficient to demonstrate a correlation of over 0.7 between $EtCO_2$, ERO_2, VO_2, DO_2, and CO. Fifty-five patients were therefore recruited, taking into account the exclusion criteria. The variables' distribution was assessed using a Kolmogorov–Smirnov test. Data are expressed as the proportion (in %), the mean (standard deviation, SD) or the median (interquartile range), as appropriate. We measured the magnitude of $EtCO_2$ variations during VE by calculating the effect size (the mean divided by the SD).[18,19] The effect size was 0.74. Then, we calculated the coefficient of variation (CV), precision and least significant change (LSC) for $EtCO_2$. LSC is the least amount of $EtCO_2$ change that can be considered statistically significant; that is, the minimum percentage change between successive measurements that can be considered not due to random error and therefore representing a real change in $ETCO_2$. The $EtCO_2$ CV and LSC were determined in all studied patients at baseline

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during stable respiratory and hemodynamic conditions. The CV (95% confidence interval [CI]) was 1.8% (0.9–2.7) and the LSC (95% CI) was 2.5% (1.3–3.8). $EtCO_2$ responder was defined as an increase of $EtCO_2$ of more than 4% in $EtCO_2$ after VE. $EtCO_2$ nonresponder was defined as an increase of $EtCO_2$ of <4% in $EtCO_2$ after VE. This cut off correspond to LSC with its 95% CI.[20] Fluid responder was defined as an increase of more than 15% in the SV during VE.[21] Fluid nonresponder was defined as an increase of <15% in the SV during VE. The nonparametric Wilcoxon rank sum test, Student paired *t* test, Student *t* test, and the Mann–Whitney test were used to assess statistical significance, as appropriate. Linear correlations were tested using Pearson or Spearman rank method. A receiver-operating characteristic curve was established for $EtCO_2$, with a view to predicting a decrease of over 10% in O_2ER, and a increase over 10% in $ScVO_2$.[22] The threshold for statistical significance was set to $P < 0.05$. SPSS software (version 21, IBM, New York, NY) was used to perform statistical analysis.

RESULTS

Fifty-one postoperative patients were analyzed after inclusion in the study (Figure 1, Table 1). The indications for VE were as follows: arterial hypotension (n = 34), oliguria (n = 4), and clinical signs of hypoperfusion (n = 13). Eighteen (35%) patients had hyperlactatemia. Indications for VE did not differ between $EtCO_2$ responders and $EtCO_2$ nonresponders ($P > 0.05$). Twenty (39%) of the 51 patients were classified as $EtCO_2$ responders. All $EtCO_2$ responders were also fluid responders and displayed a mean (95% CI) $EtCO_2$ of 7% (6–9) during VE (Figure 1). Thirty-one patients were classified as $EtCO_2$ nonresponders and displayed a mean (95% CI) change in $EtCO_2$ of 0% (−1 to 1) during VE (Figure 1). Twenty-six of the $EtCO_2$ nonresponders were fluid responders and 5 were fluid nonresponders. At baseline, prevalence of norepinephrine treatment did not differ between the 2 groups of patients (12 [39%] $EtCO_2$ nonresponders vs 7 [35%] $EtCO_2$ responders, $P = 0.1$). At baseline, SV variations with PLR did not differ between $EtCO_2$ responders and $EtCO_2$ nonresponders ($P > 0.05$, Table 2).

Effect of VE on Hemodynamic and Blood Gas Parameters

In the study population as a whole, VE led to increases in MAP, CVP, SV, CO, $EtCO_2$, DO_2, PvO_2, and $ScvO_2$, and decreases in HR, $PvCO_2$, O_2ER, and alveolar dead space (Tables 2 and 3). At baseline, MAP, PvO_2, and $ScvO_2$ were lower and VO_2 and O_2ER were higher in $EtCO_2$ responders than in $EtCO_2$ nonresponders (regardless of the presence or absence of a fluid response in the latter; Tables 2 and 3).

In $EtCO_2$ nonresponders, VE led to increases in MAP, SV, CO, CVP, DO_2, and VO_2. $PvCO_2$ decreased during VE. In $EtCO_2$ responders, VE led to increases in MAP, SV, CO, CVP, $EtCO_2$, PvO_2, DO_2, and $ScvO_2$ and decreases in $PvCO_2$, $PcCO_2$ gap, O_2ER, and alveolar dead space (Tables 2 and 3).

Correlations Between Hemodynamic, Blood Gas Parameters, and $EtCO_2$

In the overall population at baseline, $EtCO_2$ was correlated with CO, DO_2, and O_2ER ($r = 0.48$, $P = 0.001$; $r = 0.47$, $P = 0.001$; and $r = -0.42$, $P = 0.005$, respectively). O_2ER was not correlated with arterial lactate levels ($r = 0.01$, $P = 0.99$ but was correlated with $PavCO_2$ ($r = -0.46$, $P = 0.01$). Changes in $EtCO_2$ during VE were correlated with those in CO, PvO_2, DO_2, VO_2, $ScVO_2$, and O_2ER (Table 4). A change of more than 4% in $EtCO_2$ during VE predicted a decrease of more than 10% in the VO_2/DO_2 ratio with an area under the curve (95% CI) of 0.88 (0.77–0.96) ($P < 0.0001$), a sensitivity of 71% (53–85), a specificity of 94% (71–100), a positive likelihood ratio of 12, negative likelihood ratio of 0.31, a positive predictive value of 96,

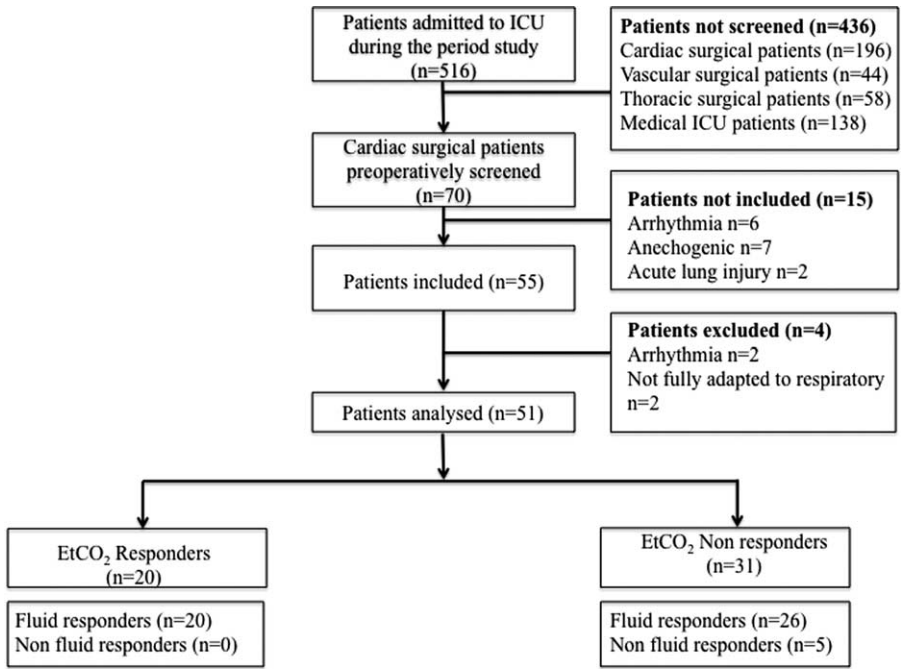

FIGURE 1. Study flow chart.

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TABLE 1. Characteristics of the Study Participants on Inclusion

Age, mean (SD), y	70 (11)
Gender, F/M	16/35
Heart surgery, n (%)	
Valve replacement	22 (43)
CABG	15 (29)
Mixed	7 (14)
Other (aortic dissection, atrial myxoma)	7 (14)
Respiratory parameters	
Tidal volume, mL/kg of predicted body weight	7.8 (0.5)
Respiratory rate, per min	17 (2)
Plateau pressure, cm H_2O	18 (3)
Total PEEP, cm H_2O	7 (2)
Left ventricular ejection fraction, n (%)	48 (12)
Patients treated with norepinephrine, n (%)	19 (37)

Values are expressed as the mean ± SD or the number (%).
CABG = coronary artery bypass graft, PEEP = positive end-expiratory pressure, SD = standard deviation.

and a negative predictive value of 62. In the same way, change in $EtCO_2$ during VE predicted an increase of more than 10% in $ScVO_2$ with an area under the curve (95% CI) of 0.90 (0.78–0.97), $P < 0.0001$.

DISCUSSION

Our results demonstrated that during VE, the occurrence of concomitant increases in $EtCO_2$ and CO depends on the relationship between VO_2 and DO_2; an increase in CO was not necessarily accompanied by an increase in $EtCO_2$. Only patients with a high extraction ratio (i.e., low $ScvO_2$ values) will display an increase in $EtCO_2$. Thus, changes in $EtCO_2$ during VE reflect changes in O_2ER in response to a rise in DO_2. Hence, during VE, $EtCO_2$ may be a useful noninvasive indicator of changes in systemic oxygen supply dependency when fixed ventilation is maintained.

Several preclinical and clinical studies have demonstrated that $EtCO_2$ can be used as a noninvasive, continuous measure of CO during low-flow states (cardiac arrest, hemorrhagic shock, cardiopulmonary resuscitation, circulatory shock, etc.).[9–11] Similarly, $EtCO_2$ has been shown to reflect changes in VO_2 and VCO_2 during hemorrhagic shock.[12,13] Our present results demonstrated that $EtCO_2$ may reflect changes in systemic oxygen supply associated with changes in CO during VE in nonseptic patients. All the patients in our study were postoperative sedated and nonhypothermic. Alveolar ventilation procedures and norepinephrine dosage did not change over the study period, and CO increased during VE. Even then, only 50% of fluid responders displayed an increase in $EtCO_2$, thus $EtCO_2$ was poorly correlated with changes in CO. Our results confirm previous findings in the operating theatre, where $EtCO_2$ and CO were rather low.[14] To determine the mechanisms by which increase in CO increase $EtCO_2$ during VE, 1 would have to consider the study population and the effects of increase CO on blood gas parameters.

At baseline, $EtCO_2$ responders had a lower MAP than $EtCO_2$ nonresponders, whereas the 2 groups did not differ significantly in terms of preload status (i.e., variations in SV during PLR) and CO. Although $EtCO_2$ responders and $EtCO_2$ nonresponders did not differ in terms of DO_2, the $EtCO_2$ responders had a higher VO_2 and thus a higher O_2ER and lower $ScVO_2$. VE led to an increase in CO (and thus DO_2) and a decrease in $PvCO_2$ in fluid responders. Nevertheless, VE in $EtCO_2$ responders led to a recovery of DO_2 in consistent with oxygen needs: the decrease in O_2ER resulted in an increase in PvO_2 and $ScvO_2$. In contrast, $EtCO_2$ nonresponsiveness was associated with an increase in DO_2 and VO_2 because baseline

TABLE 2. Comparison of Hemodynamic Parameters in Nonresponders, $EtCO_2$ Nonresponders, and $EtCO_2$ Responders

	$EtCO_2$ Nonresponders (n = 31)	$EtCO_2$ Responders (n = 20)
Body temperature, °C	36.6 (36.1–37.1)	36.5 (36.2–36.9)
Variation of SV with PLR, %	14 (3–24)	18 (5–29)
HR, beats/min		
Baseline	84 (20)	82 (20)
After VE	83 (19)*	79 (18)*
MAP, mm Hg		
Baseline	73 (11)	64 (16)†
After VE	80 (13)*	81 (12)*
CVP, mm Hg		
Baseline	9 (5–13)	7 (3–11)
After VE	11 (5–17)*	11 (7–13)*
SV, mL		
Baseline	40 (36–62)	43 (32–53)
After VE	53 (39–75)*	60 (39–76)*
CO, L/min		
Baseline	3.4 (2.9–4.9)	3.4 (2.5–4.5)
After VE	4.3 (3.5–5.4)*	4.5 (3.1–6.4)*
DO_2, mL/min per kg		
Baseline	6.4 (4.8–8.3)	7.2 (5.2–9.6)
After VE	7.5 (4.9–9.5)*	9.5 (6.4–11.5)*
VO_2, mL/min per kg		
Baseline	1.9 (1.4–2.3)	2.6 (1.9–3.1)†
After VE	2.1 (1.4–2.7)*	2.5 (1.6–3.2)
O_2ER		
Baseline	0.29 (0.22–0.36)	0.38 (0.29–0.49)†
After VE	0.28 (0.21–0.36)	0.29 (0.21–0.36)*
$EtCO_2$, mm Hg		
Baseline	31 (5)	26 (5)
After VE	31 (6)	29 (5)*
Alveolar dead space		
Baseline	0.21 (0.09)	0.26 (0.09)
After VE	0.2 (0.10)	0.20 (0.09)*
Arterial lactate, mmol/L		
Baseline	1.8 (1.5–2.1)	2.1 (1.6–2.7)
After VE	1.7 (1.4–2.3)	2 (1.4–2.6)

Values are expressed as the mean (standard deviation) or the median (interquartile range).
CO = cardiac output, CVP = central venous pressure, DO_2 = oxygen delivery, $EtCO_2$ = end-tidal carbon dioxide pressure, HR = heart rate, MAP = mean arterial pressure, O_2ER = oxygen extraction, PLR = passive leg raising, SV = stroke volume, VE = volume expansion, VO_2 = oxygen consumption.
*$P < 0.05$ within groups (between baseline and VE).
†$P < 0.05$ for $EtCO_2$ nonresponders vs $EtCO_2$ responders.

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TABLE 3. Comparison of Blood Gas Parameters in $EtCO_2$ Nonresponders and $EtCO_2$ Responder Groups

	$EtCO_2$ Nonresponders (n = 31)	$EtCO_2$ Responders (n = 20)
Hemoglobin, g/dL		
Baseline	10.9 (1.5)	11.8 (1.4)
After VE	10.7 (1.5)*	11.2 (1.3)*
SaO_2, %		
Baseline	97.6 (1.7)	98.2 (1.1)
After VE	97.9 (1.5)	98.1 (1.3)
SvO_2, %		
Baseline	68.9 (9.2)	59.9 (10.5)†
After VE	70.1 (10.2)	70.3 (10.6)*
PaO_2, mm Hg		
Baseline	126 (96–152)	121 (114–149)
After VE	126 (92–152)	124 (110–151)
PvO_2, mm Hg		
Baseline	40 (37–44)	35 (29–42)†
After VE	40 (37–45)	40 (34–47)*
$PaCO_2$, mm Hg		
Baseline	39 (6)	36 (6)
After VE	39 (5)	36 (6)
$PvCO_2$, mm Hg		
Baseline	47 (6)	47 (7)
After VE	46 (5)*	45 (7)*
pCO_2 gap, mm Hg		
Baseline	8 (5–10)	11 (9–13)†
After VE	6 (4–9)	9 (6–11)*
CaO_2, mL		
Baseline	14.6 (2.1)	15.9 (1.9)
After VE	14.4 (2.2)*	15 (1.7)*
CvO_2, mL		
Baseline	10.3 (2.2)	9.8 (2.3)
After VE	10.4 (2.5)	10.8 (2.1)*
$DavO_2$, mL		
Baseline	4.3 (1.4)	6.1 (1.6)†
After VE	4 (1.3)*	4.2 (1.7)*
$CaCO_2$, mL		
Baseline	51 (6.1)	49.8 (7.9)
After VE	51.3 (6.2)	49 (7.0)
$CvCO_2$, mL		
Baseline	55.2 (5.6)	55.5 (9.2)
After VE	53.6 (6.8)	52.3 (7.5)

Values are expressed as the mean (standard deviation) or the median (interquartile range).

$CaCO_2$ = arterial CO_2– contents, CaO_2 = arterial O_2 contents, $CvCO_2$ = venous CO_2 contents, CvO_2 = venous O_2 contents, $DavO_2$ = arterio-venous O2 content difference, $EtCO_2$ = end-tidal carbon dioxide tension, $PaCO_2$ = carbon dioxide arterial pressure, PaO_2 = oxygen arterial pressure, pCO_2 gap = central venous-arterial pCO_2 difference, $PvCO_2$ = carbon dioxide venous pressure, PvO_2 = oxygen venous pressure, SaO_2 = arterial oxygen saturation, SvO_2 = central venous oxygen saturation, VE = volume expansion.

*$P < 0.05$ within groups (between baseline and VE).

†$P < 0.05$ for $EtCO_2$ nonresponders vs $EtCO_2$ responders.

TABLE 4. Correlations Between Variations in $EtCO_2$, Hemodynamic Parameters, and Blood Gas Parameters During VE

	Variation in $EtCO_2$	
	r (95% CI)	*P* Value
Variation in CO	0.54 (0.35–0.73)	0.0001
Variation in PaO_2	−0.15 (−0.41 to −0.13)	0.2800
Variation in PvO_2	0.75 (0.59–0.85)	0.0001
Variation in $PaCO_2$	0.17 (−0.11 to 0.42)	0.2400
Variation in $PvCO_2$	−0.25 (−0.49 to −0.03)	0.0700
Variation in DO_2	0.39 (0.13–0.61)	0.0040
Variation in VO_2	−0.33 (−0.59 to −0.13)	0.0050
Variation in O_2ER	−0.75 (−0.85 to −0.6)	0.0001
Variation in $ScVO_2$	0.84 (0.73–0.91)	0.0001

CI = confidence interval, CO = cardiac output, DO_2 = oxygen delivery, $EtCO_2$ = end-tidal carbon dioxide tension, O_2ER = oxygen extraction ratio, $PaCO_2$ = carbon dioxide arterial pressure, PaO_2 = oxygen arterial pressure, $PvCO_2$ = carbon dioxide venous pressure, PvO_2 = oxygen venous pressure, $ScVO_2$ = central venous saturation, VE = volume expansion, VO_2 = oxygen consumption.

O_2ER did not rise. Thus, concomitant increases in $EtCO_2$ and CO may result from several different mechanisms.

Under steady-state conditions, alveolar CO_2 elimination and therefore $EtCO_2$ depend on several factors: CO_2 production (VCO_2, due to metabolism), alveolar ventilation (mechanical ventilation), pulmonary perfusion (CO), and V/Q matching. VCO_2 depends on pulmonary elimination and metabolic production of CO_2. The changes in $EtCO_2$ in our population could not be explained by metabolic production of CO_2 for several reasons. In a model of hemorrhagic shock, Dubin et al[13] demonstrated that VCO_2 could decrease $EtCO_2$ during the period of VO_2 supply dependency at low CO. The alterations in VCO_2 were statistically significant for changes in CO, DO_2, and VO_2 values that were greater than those observed in our study. A further mechanism might be related to removal of peripheral tissue CO_2 produced under anaerobic conditions.[23] In the present study, the baseline O_2ER values were below critical literature values at which tissue hypoxia was associated with anaerobic metabolism.[24] Moreover, no inter and intra group difference was shown for $CaCO_2$ and $CvCO_2$. One can hypothesize that decrease (increases) in O_2ER ($ScVO_2$) and CO will decrease the venous blood's capacity to carry CO_2 at a given PvO_2, which in turn will offset the increase in CO_2 delivery when CO rises.[25]

Thus, an increase in DO_2 may decrease $PvCO_2$ and increase CO_2 delivery to the lung. At the same time, alveolar Vd/Vt fell in $EtCO_2$ responders (despite constant minute ventilation) as a result of 2 mechanisms. The increases in PvO_2 and CO may have improved alveolar perfusion pressure and the ventilation–perfusion ratio of the lung, which would tend to decrease $PaCO_2$.[26,27] In our population, changes in $EtCO_2$ had good correlation with changes in PvO_2 and $ScVO_2$ whereas they were not associated to those in $PaCO_2$ or $PvCO_2$. These mechanisms may explain (at least in part) why $EtCO_2$ did not change in $EtCO_2$ nonresponders, whereas CO did.

In summary, $EtCO_2$ responders had a low DO_2 with regard to their VO_2 resulting in higher O_2ER (lower $ScVO_2$). VE restored the relationship between VO_2/DO_2 through CO changes and increasing PvO_2 and CO_2 delivery to the lung, which improved the patients' ventilation–perfusion ratio and thus increased $EtCO_2$.

The present study had a number of limitations. The study population (patients after heart surgery) may have differed

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from septic shock patients. Most of our patients suffered from acute circulatory failure as a result of perioperative hypovolemia, whereas septic patients generally have acute circulatory failure that combines hypovolemia, changes in microvascular perfusion and cellular dysoxia. A patient's response to VE, the relationship between DO_2 and VO_2, and the extent of anaerobic metabolism may depend on the etiology of acute circulatory failure.[28–30] We measured blood gas parameters from a central venous catheter and not from a pulmonary artery catheter. Although $ScVO_2$ cannot give a precise absolute estimate of SvO_2, it can serve as a guide to changes in SvO_2 and VO_2.[30,31] Monnet et al used blood gas parameters from a central venous catheter to assess VO_2, DO_2, and their changes over time during fluid expansion in septic patients.[31] In our study, changes in $ScVO_2$ (measured) and O_2ER (calculated) had good correlation ($r = -0.89, P < 0.0001$). Moreover, predictive values of $EtCO_2$ changes during VE did not differ to predict an increase of $ScVO_2$ or a decrease of VO_2/DO_2 ratio. Since we performed repeated measurements of blood gas levels, mathematical coupling cannot be ruled out. But De Backer et al demonstrated that during controlled conditions, VO_2 calculated from hemodynamic data is a valid alternative to VO_2 derived from respiratory gas measurements.[30,32] The method used to calculate alveolar dead space was not standardized and may have introduced bias into the determination. The difference between $EtCO_2$ and $PaCO_2$ is altered in patients with altered ventilation/perfusion ratios (due to atelectasis, chronic heart failure, acute respiratory distress syndrome, etc.). In the present study, patients with chronic pulmonary disease or acute lung injury were excluded to limit this bias. Furthermore, these results cannot be extrapolated to $EtCO_2$ changes that result from the administration of vasopressor drugs.[33] $EtCO_2$ changes seem small but they are similar to those used to predict fluid responsiveness.[34] Lastly, given that we did not measure VCO_2, we cannot rule out the occurrence of changes in metabolic production of CO_2 during the VE-induced increase in CO.

CONCLUSIONS

During VE, an increase in CO was not necessarily accompanied by an increase in $EtCO_2$. Only patients with a high O_2ER (i.e., low $ScvO_2$ values) display an increase in $EtCO_2$. Thus, $EtCO_2$ changes during fluid challenge predict changes in O_2ER (i.e., $ScVO_2$) in response to an increase in DO_2. $EtCO_2$ may be a useful noninvasive indicator of changes in systemic oxygen supply dependency in operative patients when fixed ventilation is maintained.

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