The Sensitivity and Specificity of Pulmonary Carbon Dioxide Elimination for Noninvasive Assessment of Fluid Responsiveness

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BACKGROUND: We sought to determine whether the response of pulmonary elimination of CO_2 (V_{CO_2}) to a sudden increase in positive end-expiratory pressure (PEEP) could predict fluid responsiveness and serve as a noninvasive surrogate for cardiac index (CI).
METHODS: Fifty-two patients undergoing cardiovascular surgery were included in this study. By using a constant-flow ventilation mode, we performed a PEEP challenge of 1-minute increase in PEEP from 5 to 10 cm H_2O. At PEEP of 5 cm H_2O, patients were preloaded with 500 mL IV saline solution after which a second PEEP challenge was performed. Patients in whom fluid administration increased CI by ≥15% from the individual baseline value were defined as volume responders. Beat-by-beat CI was derived from arterial pulse contour analysis, and breath-by-breath V_{CO_2} data were collected during the protocol. The sensitivity and specificity of V_{CO_2} for detecting the fluid responders according to CI was performed by the receiver operating characteristic curves.
RESULTS: Twenty-one of 52 patients were identified as fluid responders (40%). The PEEP maneuver before fluid administration decreased CI from 2.65 ± 0.34 to 2.21 ± 0.32 L/min/m^2 ($P = 0.0011$) and V_{CO_2} from 150 ± 23 to 123 ± 23 mL/min ($P = 0.0036$) in responders, whereas the changes in CI and V_{CO_2} were not significant in nonresponders. The PEEP challenge after fluid administration induced no significant changes in CI and V_{CO_2}, in neither responders nor nonresponders. PEEP-induced decreases in CI and V_{CO_2} before fluid administration were well correlated ($r^2 = 0.75$, $P < 0.0001$) but not thereafter. The area under the receiver operating characteristic curves for a PEEP-induced decrease in ΔCI and ΔV_{CO_2} was 0.99, with a 95% confidence interval from 0.96 to 0.99 for ΔCI and from 0.97 to 0.99 for ΔV_{CO_2}. During the PEEP challenge, a decrease in V_{CO_2} by 11% predicted fluid responsiveness with a sensitivity of 0.90 (95% confidence interval, 0.87–0.93) and a specificity of 0.95 (95% confidence interval, 0.92–0.98).
CONCLUSIONS: PEEP-induced changes in V_{CO_2} predicted fluid responsiveness with accuracy in patients undergoing cardiac surgery. (Anesth Analg 2016;122:1404–11)

The routine assessment of fluid responsiveness (i.e., the identification of patients in whom IV fluids will increase cardiac index [CI]) is the basis of any goal-directed fluid therapy aimed at both optimizing volemia and avoiding the deleterious consequences of fluid overload in patients undergoing surgery.[1–5]

Nowadays it is well accepted that dynamic assessments are more reliable in predicting fluid responsiveness than static parameters, such as cardiac filling pressures.[6–8] An ideal dynamic technique for preload assessment would be one performed in a simple, noninvasive, and real-time manner. Monge et al.[9] and Monnet et al.[10] have recently described such a dynamic approach by using the end-tidal carbon dioxide (P_{ETCO_2}) as a noninvasive surrogate for changes in CI induced by the passive leg-raising test. The rationale of this approach is based on the known dependency of P_{ETCO_2} on CI as observed during pulmonary embolism or cardiopulmonary resuscitation.[11–13]

In this study, we propose another dynamic approach that consists of (1) a fast-step increment in positive end-expiratory pressure (PEEP) to challenge the cardiovascular system sufficient to unmask hidden preload dependency[14–19] and (2) the evaluation of the effects of this maneuver on the amount of CO_2 exhaled during 1 minute (V_{CO_2}) obtained by volumetric capnography. We hypothesized that V_{CO_2} should be a more reliable approximation of CI than the singular P_{ETCO_2}, because V_{CO_2} has a dimension of flow just like CI.[20–22] Thus, the aim of this study was to determine the diagnostic accuracy of V_{CO_2} to detect the fluid responsiveness during a 1-step increment in PEEP in comparison with the clinical reference parameter CI.

METHODS

The study was performed in the operating theater of the Hospital Privado de Comunidad with the approval of our IRB and after obtaining written informed consent from each patient. We prospectively included a series of patients older than 40 years scheduled for programmed cardiac surgery with a New York Heart Association classification status II to III. Exclusion criteria were the presence of acute pulmonary diseases, decompensated heart failure, cardiac arrhythmias,

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Accepted for publication August 27, 2015.

Funding: None.

Conflict of Interest: See Disclosures at the end of the article.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0000000000001047

contraindication for femoral artery catheterization, and the use of aortic balloon counterpulsation.

Anesthesia and Ventilation

A 5F femoral artery catheter (PV2015L20, Pulsion Medical Systems, Munich, Germany) and peripheral and internal jugular venous cannulas were inserted under local anesthesia. Electrocardiogram, time-based capnography, pulse oximetry, and esophageal temperature were recorded by the monitor S/5 (Datex-Ohmeda, Helsinki, Finland). Anesthesia was induced with 1 to 1.5 mg/kg propofol, 0.08 mg/kg vecuronium, and 10 μg/kg fentanyl and maintained with isoflurane of 0.5 to 0.7 minimum alveolar concentration and 0.5 μg/kg/h remifentanil. Continuous IV infusions of both 3 mL/kg/h saline and 3 to 5 μg/kg/h dopamine were maintained throughout the study.

The lungs were ventilated in a volume-controlled mode of ventilation through a cuffed endotracheal tube using the Advance workstation (GE Healthcare, Madison, WI) with the following baseline settings: tidal volume (VT) 7 mL/kg of lean body weight, respiratory rate 15 breaths per minute, PEEP 5 cm H_2O, I:E ratio 1:2 without inspiratory pause, and F_{IO_2} 0.5.

Hemodynamic Measurements

The PiCCO2 Science (Pulsion Medical Systems) was used to measure CI by transthoracic thermodilution, injecting 15 mL of cold saline into the central venous catheter and recording the change in temperature with thermistors placed at the injection site and at the tip of the femoral catheter. After calibration with 3 stable thermodilutions performed by the same investigator, CI was then calculated automatically by analyzing, beat by beat, the contour of the femoral arterial pressure wave.[23] The precision of these measurements was calculated as twice their coefficient of variation (CV = SD/mean) determined in patients at baseline during stable hemodynamic and respiratory conditions. The least significant change (LSC) is defined as the minimum change in successive CI measurements that can be considered not to be due to random error and therefore represents a real change. LSC was calculated as precision × $\sqrt{2}$.[24]

Mean systemic arterial pressure, central venous pressure (CVP), and heart rate were measured continuously.

Pulse pressure variation (PPV) was calculated on a beat-by-beat basis as follows:

$$\mathrm{PPV}\ (\%) = 100 \times \left(\frac{[\mathrm{PPmax} - \mathrm{PPmin}]}{[\{\mathrm{PPmax} + \mathrm{PPmin}]\}2]} \right),$$

where PPmax and PPmin are the maximal and minimal pulse pressure values, respectively, determined over a single respiratory cycle.

Volumetric Capnography and Respiratory Measurements

Volumetric capnography was obtained from the NICO monitor and recorded on a laptop using the software DataColl (both, Respironics, Wallingford, CT). The software Flowtool (Respironics) was used to analyze the NICO raw data and to generate the CO_2 database. The NICO's mainstream CO_2 and flow sensors were placed at the airway opening after zeroing them according to the manufacturer's guidelines. The device provides the CO_2 eliminated per minute (V_{CO_2}, in mL/min) by multiplying the area under the receiver operating characteristic (ROC) curve (AUC) of the volumetric capnography by the respiratory rate.[25] The P_{ETCO_2} corresponds to the last expired CO_2 value on the capnography before the next inspiration. We calculated the precision and LSC for V_{CO_2} and P_{ETCO_2} in all patients during stable baseline hemodynamic and respiratory conditions.[24]

Study Design

Figure 1 shows a schematic representation of the protocol, which was performed with patients in the supine position before surgery with the chest closed. After anesthesia induction, the lung's volume history was standardized by ventilating each patient at a PEEP of 10 cm H_2O and a VT of 10 mL/kg for 10 breaths before returning to baseline settings. After calibration, CI was determined continuously by automatic pulse contour analysis rather than by repeated discontinuous manual thermodilutions. This was because the latter are time consuming and not representative of the fast and transient beat-by-beat changes in CI induced by the brief PEEP challenge.

The protocol was performed according to the following sequence (Fig. 1): First, 3 manual thermodilutions were done to calibrate the CI measurements (asterisk). Then, at baseline, ventilation was performed as described in Anesthesia and Ventilation, and data were recorded for 5 minutes. After 3 minutes at PEEP 5 cm H_2O, the PEEP challenge consisting of a sudden increase in PEEP from 5 to 10 cm H_2O for 1 minute was performed with return to baseline PEEP 5 cm H_2O.

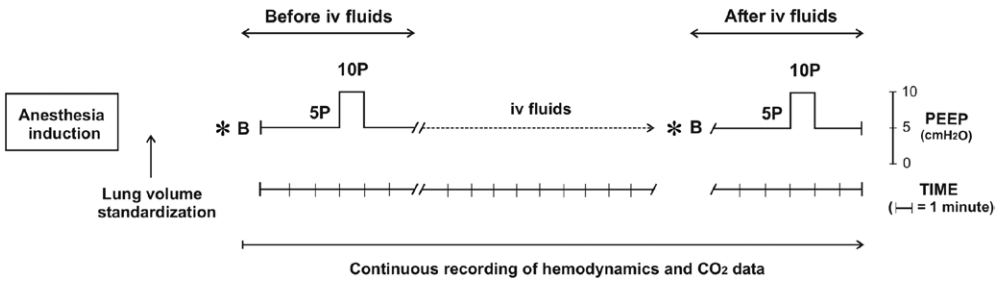

Figure 1. Schematic protocol. The protocol was executed in a closed chest condition after anesthesia induction. Asterisks mark times of calibrations of pulse contour cardiac index using triplicate transthoracic thermodilutions. B is the baseline condition before and after fluid administration. PEEP challenges—consisting of a sudden increment from 5 to 10 cm H_2O of PEEP for just 1 minute—were performed before and after fluid administration (see text for more details). PEEP = positive end-expiratory pressure.

This sequence was repeated after infusing 500 mL of saline solution over 10 minutes.

Data Analysis

Hemodynamics and CO_2 data were analyzed offline by coauthors blinded to the results of this study. Patients in whom fluid administration increased CI by ≥15 % from the individual baseline value were defined as volume responders and the remaining ones as nonresponders. This cutoff value was justified by the fact that the LSC of CI measured by thermodilution was 12% when 3 optimum measurements were averaged.[26] To confirm this cutoff in our study population, we ensured that every responding patient increased CI above his or her individual LSC value.[9,24]

During each study period, the last 4 breaths were analyzed. This standardized selection of breaths is of particular importance for the PEEP challenges because the increase in PEEP from 5 to 10 cm H_2O induced parallel changes in VT, P_{ETCO_2}, and V_{CO_2}, which were, however, limited to the first 5 to 7 breaths of each study period (Fig. 2).[27]

Statistical analysis was performed using IBM SPSS Statistic 19.0.0 (IBM Corp., Armonk, NY) and MATLAB® (Mathworks, Natick, MA). Sample size was calculated to detect differences of 0.10 with an expected AUC curve of 0.85. We selected a type I error of 0.05 and a type II error of 0.02 assuming that fluid responsiveness occurs in 50% of patients undergoing cardiac surgery.[19,28]

Normal distribution of data was tested using the Lilliefors test. CVP, heart rate, and PPV showed a nonnormal distribution in some protocol steps; therefore, a nonparametric 2-sample Kolmogorov–Smirnov test was applied for pairwise comparison of values between study periods. Linear regression analysis between all the variables studied was performed. Areas under the ROC curves for volume-induced changes in CI, V_{CO_2}, P_{ETCO_2}, and PPV were calculated and compared by using the Hanley–McNeil test. Results are expressed as mean ± SD, median and interquartile range, or 95% confidence interval as appropriate. A P value <0.05 was considered statistically significant.

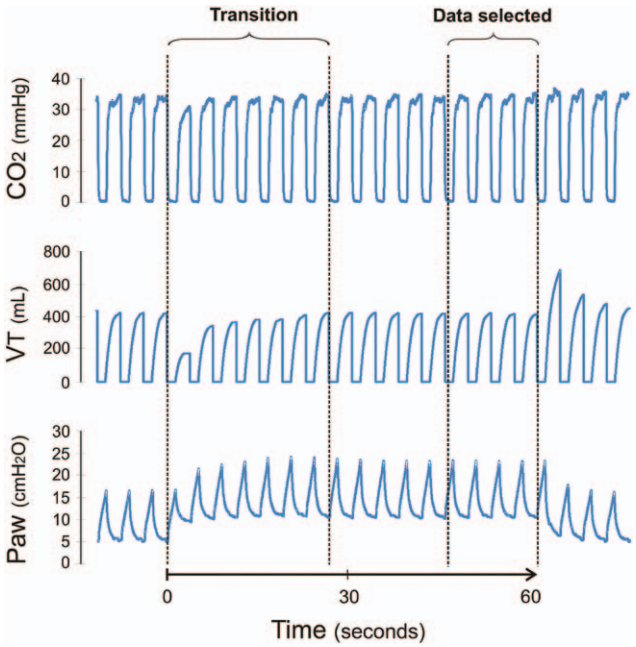

Figure 2. Schematic representation of data selection during the positive end-expiratory pressure (PEEP) challenge. Representative recording of carbon dioxide, tidal volume (VT), and airway pressure (Paw) during a PEEP challenge. Transition: As PEEP changes from 5 to 10 cm H_2O, lung volume increases by preventing inspired gas from leaving the lungs. During 5 to 7 successive breaths, CO_2 elimination decreases because of both decreasing expired VTs and a transient dilution of the CO_2 stored within the lungs by CO_2-free inspired gases. Therefore, only the last 4 breaths of the new equilibrium were analyzed (data selected).

RESULTS

From June 1, 2012, to August 31, 2013, we studied 52 patients undergoing cardiac surgery whose demographic characteristics are shown in Table 1. One patient was dropped from the analysis because of missing hemodynamic data of the PICCO device. Precision and LSC was 2.1% ± 0.2% and 2.9% ± 2.6% for pulse contour CI, 1.4% ± 0.7% and 2.1% ± 1.0% for V_{CO_2}, and 1.2% ± 0.6% and 1.7% ± 0.8% for P_{ETCO_2}.

Effects of Fluid Administration at Baseline Conditions

Twenty-one patients (40%) were volume responders when baseline data were compared before and after fluid administration. Table 2 presents the effect of volume expansion on the study parameters, and Figure 3 illustrates this effect on the studied CO_2-derived variables. Volume responders increased CI from 2.65 ± 0.33 to 3.29 ± 0.40 L/mi/m^2 (P < 0.0001), V_{CO_2} and P_{ETCO_2} did not show significant changes, whereas PPV decreased from 9.1% ± 2.5% to 6.3% ± 3.1 % (P = 0.0036) after fluid administration with all

Table 1. Characteristics of the Study Population

Age (yr)	70 ± 6
Weight (kg)	82 ± 17
Sex (male)	38 (73%)
Height (cm)	170 ± 11
BMI (kg/m^2)	28 ± 9
EF (%)	51 ± 10
NYHA	2 (2–3)
Type of surgery, absolute value (%)	
CABG	42 (81)
Valvular repair	10 (19)
Both	3 (6)
Chronic diseases, absolute value (%)	
Hypertension	31 (60)
AMI	10 (19)
CCF	5 (9)
Diabetes	23 (44)
COPD	18 (34)
Ex-smoking	40 (76)
CRF	4 (8)
Obesity	20 (38)
Preoperatory drugs, absolute value (%)	
β-Blockers	21 (40)
Vasodilators	25 (49)
Diuretics	17 (33)

Quantitative data are presented as mean ± SD except for NYHA (median and first to third interquartile). Qualitative data are presented as absolute values: number of patients (% of total).

AMI = acute myocardial infarction; BMI = body mass index; CABG = coronary artery bypass graft; CCF = chronic cardiac failure; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; EF = ejection fraction; NYHA = New York Heart Association classification status.

Table 2. Hemodynamic Data

	Before IV fluids			After IV fluids		
Parameter	**Baseline**	**5 PEEP**	**10 PEEP**	**Baseline**	**5 PEEP**	**10 PEEP**
CI (L/min/m²)						
Responders	2.65 ± 0.33	2.64 ± 0.34	2.21 ± 0.32	3.29 ± 0.40	3.28 ± 0.47	3.13 ± 0.44
Nonresponders	2.94 ± 0.50	2.92 ± 0.48	2.73 ± 0.47	3.13 ± 0.53	3.08 ± 0.55	2.95 ± 0.52
a	*P* = 0.0420	*P* = 0.0420	*P* = 0.0032	*P* = 0.0198		
b (R)				*P* < 0.0001		
c (NR)			*P* = 0.0011			
HR (bpm)						
Responders	70 ± 17	69 ± 16	70 ± 18	69 ± 14	68 ± 15	68 ± 16
Nonresponders	73 ± 13	72 ± 13	71 ± 14	70 (58.5–84)	70 ± 13	69 ± 14
MAP (mm Hg)						
Responders	78 ± 15	75 ± 14	62 ± 13	87 ± 15	88 ± 16	86 ± 15
Nonresponders	82 ± 11	80 ± 10	75 ± 13	84 ± 12	84 ± 10	81 ± 11
a			*P* = 0.0037		*P* = 0.0455	
c (R)			*P* = 0.0036			
CVP (mm Hg)						
Responders	10 ± 4	10 ± 3	12 ± 3	12 ± 4	12 ± 3	13 ± 3
Nonresponders	10 ± 4	11 ± 4	11.5 (8–15)	11.5 (9–14)	12 ± 3	13 (9–15)
PPV (%)						
Responders	9.1 ± 2.5	10 (7–10)	14.6 ± 4.4	6.3 ± 3.1	6.3 ± 2.8	7.9 ± 3.0
Nonresponders	8.7 ± 3.6	9 (6–12)	11.9 ± 4.4	6.5 ± 2.8	6.9 ± 3.2	8.2 ± 2.8
b (R)				*P* = 0.0036		
b (NR)				*P* = 0.0299		
c (R)			*P* <0.0001			
V_{CO_2} (mL/min)						
Responders	148 ± 24	150 ± 23	123 ± 23	159 ± 25	156 ± 24	146 ± 24
Nonreponders	159 ± 30	158 ± 30	148 ± 29	167 ± 31	165 ± 30	156 ± 29
a	*P* = 0.042		*P* = 0.0003			
c (R)			*P* = 0.0036			
P_{ETCO_2} (mm Hg)						
Responders	33.0 ± 2.4	32.5 ± 2.4	30.8 ± 2.4	33.9 ± 2.8	33.8 ± 2.7	33.2 ± 2.7
Nonresponders	34.4 ± 2.9	33.9 ± 2.7	32.9 ± 2.9	34.2 ± 3.1	34.0 ± 3.0	33.4 ± 3.0
a			*P* = 0.0087			

a: responders (R) versus nonresponders (NR); b: baseline before versus after fluid administration; c: 5-PEEP versus 10-PEEP for both, before, and after fluid administration. Results are presented in mean ± SD or median (interquartile intervals).

CI = cardiac index; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; PEEP = positive end-expiratory pressure; P_{ETCO_2} = end-tidal partial pressure of carbon dioxide; PPV = pulse pressure variation; V_{CO_2} = pulmonary elimination of carbon dioxide.

values exceeding the individual LSC values. Nonresponders showed nonsignificant changes in CI, V_{CO_2}, and P_{ETCO_2} (Table 2). PPV decreased from 8.7% ± 3.6% to 6.5% ± 2.8 % (P = 0.0299).

Taking all patients together and comparing baseline conditions before and after fluid administration, we found a weak correlation between volume-induced changes in CI (ΔCI) and V_{CO_2} (ΔV_{CO_2}; r^2 = 0.34, P < 0.0001) but no correlations at all between ΔCI and ΔP_{ETCO_2} or ΔPPV. Correlations between ΔCI and the main studied variables reached significance neither in responders nor in nonresponders.

Effects of PEEP Challenges

The first PEEP challenge before IV fluids were given, made CI drop from 2.64 ± 0.34 to 2.21 ± 0.32 L/min/m² (P = 0.0011) in responders but without significant changes in nonresponders. V_{CO_2} decreased from 150 ± 23 to 123 ± 23 mL/min (P = 0.0036) in responders. Neither V_{CO_2} nor P_{ETCO_2} showed significant changes during PEEP challenge before fluid administration in nonresponders. The increment in PPV during the first PEEP challenge was significant in responders but not in nonresponders (Table 2). A good correlation between ΔCI and ΔV_{CO_2} was found (r^2 = 0.75, P < 0.0001; Fig. 4A).

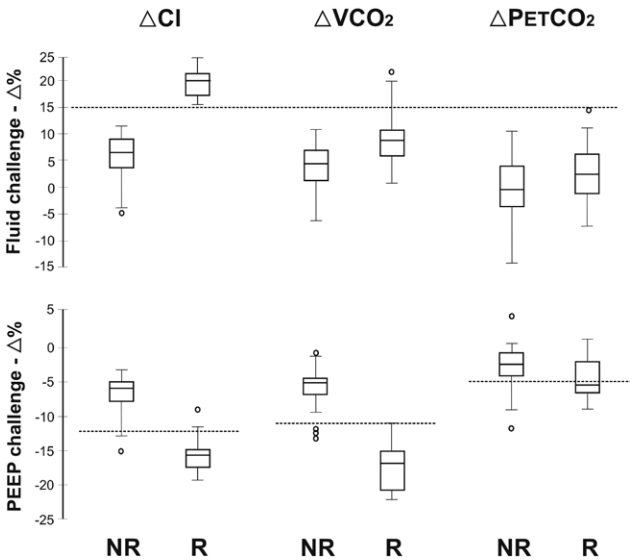

Figure 3. Box plots for responders (R) and nonresponders (NR) during the fluid challenge (upper) and during the PEEP challenge before fluids (lower). The changes in cardiac index (ΔCI), elimination of CO_2 (ΔV_{CO_2}), and end-tidal partial pressure of CO_2 (ΔP_{ETCO_2}) are presented as percentage. The dotted lines represent the threshold value of cardiac index (CI) to define R and NR (upper) or threshold values for each parameter to predict fluid responsiveness (lower). Open circles are outliers.

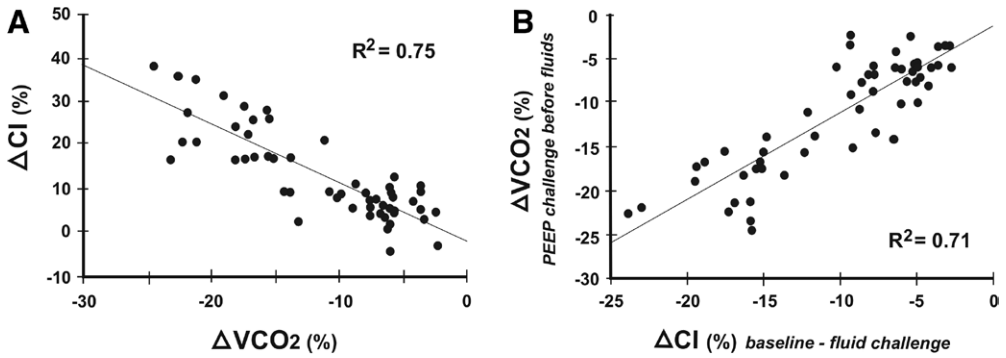

Figure 4. A, Linear regression analysis of the relationship between ΔCI and ΔV_{CO_2} during the PEEP challenge before fluid administration. B, Linear regression analysis of the relationship between ΔV_{CO_2} during the PEEP challenge before fluid administration and ΔCI induced by the fluids. ΔCI, changes in cardiac index; PEEP = positive end-expiratory pressure; ΔV_{CO_2} = elimination of CO_2.

During the second PEEP challenge after IV fluids were given, the changes in ΔCI, ΔV_{CO_2}, ΔP_{ETCO_2}, and ΔPPV were lower than before fluid administration in both responders and nonresponders. Neither of these changes was statistically significant nor was there a good correlation among them. The changes in ΔCI induced by fluid loading at baseline were well correlated with the changes in ΔV_{CO_2} induced by the first PEEP challenge before fluid administration ($r^2 = 0.71$, $P < 0.0001$; Fig. 4B).

Prediction of Fluid Responsiveness

The comparison of the predictive performance of studied parameters for detecting fluid responsiveness is given in Figure 5 and Table 3. A decrease of ≥11% in V_{CO_2} during the PEEP challenge predicted a ≥15% increase in CI after fluid administration with high sensitivity and specificity. However, a decrement by ≥5% in P_{ETCO_2} during the PEEP challenge predicted a fluid-induced increase in CI by ≥15% with a poor sensitivity and specificity. PPV had also a poor sensitivity and specificity for detecting fluid responsiveness according to the reference method.

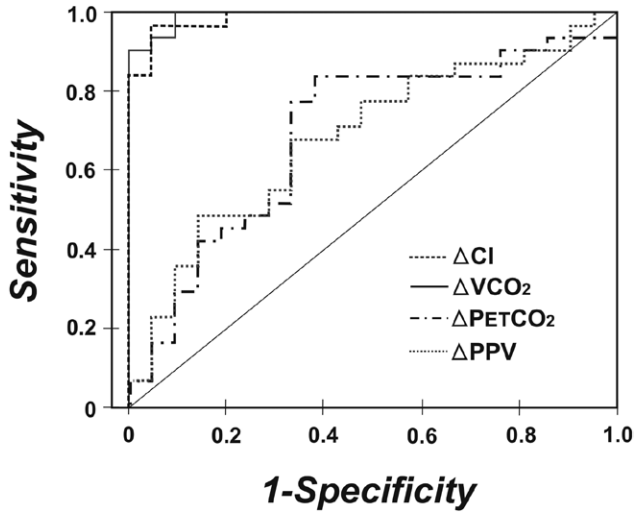

Figure 5. Receiver-operating characteristic (ROC) curves of fluid responsiveness. ROC curves for the ability of changes in the elimination of CO_2 (ΔV_{CO_2}), the end-tidal partial pressure of CO_2 (ΔP_{ETCO_2}), and pulse pressure variation (ΔPPV) during a positive end-expiratory pressure challenge to predict an increase in CI by ≥15% if fluids were given. The areas under the ΔP_{ETCO_2} and ΔPPV curve were different from ΔV_{CO_2} ($P < 0.05$).

DISCUSSION

The main finding of this study is that a decrease in V_{CO_2} observed during a brief PEEP challenge was accurate in predicting fluid responsiveness. The clinical implication of our results is that a dynamic approach using CO_2 can detect preload dependency at the bedside in a totally noninvasive way by means of a simple ventilator maneuver. Thus, the always difficult diagnosis of preload dependency could be easily established in patients in whom more invasive CI monitoring equipment is not available. This is of particular importance in the operating theater for medical, economical, and ethical reasons, because most of our patients present no clinical indication for invasive and expensive hemodynamic monitoring.

We found that 40% of our patients were fluid responders according to the standard definitions.[6–8] This result is in line with the studies by Kim et al.[28] and Preisman et al.[19] who found that the incidence of fluid responsiveness in patients undergoing cardiac surgery was 38% and 46%, respectively.

Different dynamic ventilatory maneuvers to assess fluid responsiveness in mechanically ventilated patients have been described.[29–31] These include cyclical changes during mechanical breaths or step changes in PEEP and expiratory pauses.[15–18] Based on the physiologic principles governing heart–lung interactions, these maneuvers stress the hemodynamic state reversibly without the need to administer fluids. The principle tested whether a step PEEP change is a reversible maneuver that can help detect fluid responsiveness as measured by different invasive parameters.[15,16] In experimental animals, Lambert et al.[18] found that 10 cm H_2O of PEEP affected stroke volume in proportion to the deficit in intravascular fluids. Michard et al.[16] showed that the variations in pulse pressure induced by 10 cm H_2O of PEEP were predictive of fluid responsiveness in patients with acute respiratory distress syndrome. In patients undergoing cardiac surgery, Geerts et al.[15] showed that PEEP-induced changes in CVP predicted fluid responsiveness in the same way as the combination of passive leg-rising test and CI.

Monitoring expired CO_2 is attractive because it is simple, real time, and noninvasive. The amount of eliminated CO_2 depends simultaneously and continuously on the body's metabolism, pulmonary perfusion, and alveolar ventilation.

Table 3. Predictive Performance for Detecting Fluid Responsiveness

	AUC	Threshold (%)	Sensitivity	Specificity	PV+	PV−	LR+	LR−
ΔCI	0.99 (0.96–0.99)	12	0.92 (0.85–0.97)	0.94 (0.91–0.97)	0.90 (0.85–0.96)	0.93 (0.84–0.97)	6.18 (2.63–7.80)	0.08 (0.03–0.16)
ΔVco_2	0.99 (0.97–0.99)	11	0.90 (0.87–0.93)	0.95 (0.92–0.98)	0.92 (0.85–0.96)	0.91 (0.90–0.94)	6.06 (3.33–8.00)	0.10 (0.07–0.14)
$\Delta Petco_2$	0.69 (0.62–0.76)	5	0.63 (0.49–0.75)	0.74 (0.67–0.80)	0.61 (0.55–0.66)	0.71 (0.56–0.81)	2.74 (1.51–3.90)	0.55 (0.34–0.86)
ΔPPV	0.68 (0.60–0.76)	30	0.48 (0.39–0.56)	0.75 (0.66–0.83)	0.73 (0.61–0.81)	0.46 (0.36–0.55)	1.62 (0.73–2.66)	0.79 (0.62–1.07)

Parentheses values are 95% confidence intervals. Intervals for AUC were computed using a modified Wald interval with continuity correction.[38] For sensitivity, specificity, PV+, PV−, LR+, LR−, cross-validation k-fold (k = 5), 1000 times were performed, and the 95% confidence interval was considered as the lower and upper bounds of the percentiles 2.5% and 97.5%, respectively.

AUC = area under the receiver operating characteristic curve; ΔCI = PEEP challenge-induced changes in cardiac index; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; $\Delta Petco_2$ = PEEP challenge-induced changes in end-expiratory partial pressure of CO_2; PEEP = positive end-expiratory pressure; PPV = PEEP challenge-induced changes in pulse pressure variation; PV+ = positive predictive value; PV− = negative predictive value; ΔVco_2 = PEEP challenge–induced changes in the elimination of CO_2.

Therefore, the changes in Vco_2 must be interpreted with caution.[27] When metabolic production of CO_2 and alveolar ventilation are constant during the measuring period, as in our short lasting protocol, a change in CO_2 can be explained conclusively by a parallel change in pulmonary blood flow.[20,21]

$Petco_2$ is the parameter most commonly used in time-based capnography, which has demonstrated a close association with CI in different scenarios.[11–13] However, we found a rather poor correlation between absolute and relative values of $Petco_2$ and CI after fluid administration and during the PEEP challenge. The performance of $\Delta Petco_2$ in predicting fluid responsiveness was poor in our study (AUC, 0.69; sensitivity, of 0.67; specificity, 0.77) but excellent in the studies by Monnet et al.[10] (AUC, 0.93; sensitivity, 0.71; and specificity, 1) and Monge et al.[9] (AUC, 0.94; sensitivity, 0.91; and specificity, 0.94). Despite these differences, the cutoff value for $\Delta Petco_2$ to detect fluid responsiveness was the same (5%) in all studies.

These differences in the performance of $Petco_2$ could be explained in part by differences in the patient populations studied (intensive care versus cardiac surgery patients) and by the nature of the dynamic maneuvers used to challenge the heart–lung interaction (passive leg-raising test versus PEEP test). We speculate that the degree of change in $Petco_2$ that these opposing maneuvers induce might be rather different, because the value of $Petco_2$ highly depends on the slope of phase III of the capnogram.[32–34] Increasing CI by passive leg-raising can increase the slope of phase III, and hence its final CO_2 value, the $Petco_2$.[21] Conversely, a PEEP challenge will have an opposite effect because the slope of phase III becomes flatter and thus $Petco_2$ becomes lower any time CI decreases. In other words, the positive changes in $Petco_2$ seen during the passive leg-raising test could be larger than the negative changes induced by PEEP.

Our results support the hypothesis that Vco_2 is a better capnographic-derived parameter than $Petco_2$ in predicting fluid responsiveness for the following reasons: First, the correlation between ΔCI and ΔVco_2 during the PEEP challenge before fluid administration was good, whereas the correlation between ΔCI and $\Delta Petco_2$ was poor. Second, the ΔCI induced by fluids at baseline was well correlated with the ΔVco_2 induced by the PEEP challenge before fluid administration but not with $\Delta Petco_2$ at the same instance. Furthermore, Vco_2 is obtained by volume-based, but not by time-based, capnography and thus is measured in the flow domain, the same as for CI.[35] In patients undergoing weaning from cardiopulmonary bypass, we demonstrated that Vco_2 was directly proportional to the amount of pulmonary blood flow.[20,21] The fact that the cutoff values for ΔCI and ΔVco_2 to detect fluid responsiveness were similar in our responder patients supports the existence of such a close relationship. The ROC curve confirmed the aforementioned notion, showing a higher sensitivity and specificity for ΔVco_2 than for $\Delta Petco_2$ to predict fluid responsiveness.

The observed changes in PPV, similar to Vco_2 and $Petco_2$, presented a predicted physiologic behavior during fluid and PEEP challenges in both responders and nonresponders. Even though these congruent changes in PPV were significant (Table 2), this variable was poorly correlated with CI and Vco_2 and had a limited performance in predicting fluid responsiveness in our patients (Table 3). This poor performance of PPV in defining fluid responsiveness in our study can perhaps be explained by the use of 7 mL/kg of VT. There is a trend toward decreasing intraoperative VT that limits the value of PPV as a clinical tool for monitoring in the operating room.[36,37]

Limitations

The impact of lung diseases or pulmonary shunt on our methodology is unknown, because we did not evaluate these clinical conditions separately. Vco_2 could increase with the application of 10 cm H_2O of PEEP because of a potential recruitment of small airways and atelectasis, thereby mitigating the PEEP-induced decrement in Vco_2 in responders. To eliminate this confounding factor, we standardized lung volume by applying 10 deep breaths before starting the protocol.

We can speculate that our method should also be reliable in patients with lung diseases or shunt because (1) patients served as their independent controls regardless of the underlying lung condition and (2) ΔCI, a variable hardly affected by chronic lung diseases and fixed shunt in the short run, during the first PEEP challenge changed in a similar way as ΔVco_2 (−12% vs −11%, respectively) while a good correlation between them was found (Fig. 4). This important issue should be properly tested in future studies.

CONCLUSIONS

The combination of a reversible hemodynamic challenge by PEEP in conjunction with the response in noninvasive Vco_2 may be a simple way to identify those patients undergoing cardiac surgery who could benefit from fluid administration.

DISCLOSURES

Name: Gerardo Tusman, MD.
Contribution: This author helped design the study, conduct the study, collect the data, analyze the data, and prepare the manuscript.
Attestation: Gerardo Tusman has reviewed the original study data and data analysis and is the archival author.
Conflicts of Interest: Gerardo Tusman performs consultant activities for Maquet Critical Care and is the owner of a patent on volumetric capnography.
Name: Iván Groisman, MD.
Contribution: This author helped collect the data and analyze the data.
Attestation: Iván Groisman collected and analyzed the data.
Conflicts of Interest: None.
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Contribution: This author helped collect the data.
Attestation: Gustavo A. Maidana collected the data.
Conflicts of Interest: None.
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Attestation: Adriana Scandurra did the main calculations of studied variables and the statistical analysis.
Conflicts of Interest: None.
Name: Jorge Martinez Arca, Eng.
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Attestation: Jorge Martinez Arca did the statistical analysis.
Conflicts of Interest: None.
Name: Stephan H. Bohm, MD.
Contribution: This author helped design the study and prepare the manuscript.
Attestation: Stephan H. Bohm reviewed the original study data and data analysis.
Conflict of Interest: Stephan H. Bohm is the owner of a patent on volumetric capnography.
Name: Fernando Suarez-Sipmann, PhD.
Contribution: This author helped design the study and prepare the manuscript.
Attestation: Fernando Suarez-Sipmann reviewed the original study data and data analysis.
Conflict of Interest: Fernando Suarez-Sipmann received a grant from the "Fondo de Investigación Sanitaria" Instituto de salud Carlos III. FIS-PI070136 and performed consultant activities for Maquet Critical Care.
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