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End-tidal carbon dioxide is better than arterial pressure for predicting volume responsiveness by the passive leg raising test

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Abstract Purpose: In stable ventilatory and metabolic conditions, changes in end-tidal carbon dioxide (EtCO₂) might reflect changes in cardiac index (CI). We tested whether EtCO₂ detects changes in CI induced by volume expansion and whether changes in EtCO₂ during passive leg raising (PLR) predict fluid responsiveness. We compared EtCO₂ and arterial pulse pressure for this purpose. **Methods:** We included 65 patients [Simplified Acute Physiology Score (SAPS) II = 57 ± 19, 37 males, under mechanical ventilation without spontaneous breathing, 15 % with chronic obstructive pulmonary disease, baseline CI = 2.9 ± 1.1 L/min/m²] in whom a fluid challenge was decided due to circulatory failure and who were monitored by an expiratory-CO₂ sensor and a PiCCO2 device. In all patients, we measured arterial pressure, EtCO₂, and CI before and after a fluid challenge. In 40 patients, PLR was performed before fluid administration. The PLR-induced changes in arterial pressure, EtCO₂, and CI were recorded. **Results:** Considering the whole population, the fluid-induced changes

in EtCO₂ and CI were correlated ($r^2 = 0.45$, $p = 0.0001$). Considering the 40 patients in whom PLR was performed, volume expansion increased CI ≥ 15 % in 21 “volume responders.” A PLR-induced increase in EtCO₂ ≥ 5 % predicted a fluid-induced increase in CI ≥ 15 % with sensitivity of 71 % (95 % confidence interval: 48–89 %) and specificity of 100 (82–100) %. The prediction ability of the PLR-induced changes in CI was not different. The area under the receiver-operating characteristic (ROC) curve for the PLR-induced changes in pulse pressure was not significantly different from 0.5. **Conclusion:** The changes in EtCO₂ induced by a PLR test predicted fluid responsiveness with reliability, while the changes in arterial pulse pressure did not.

Keywords Volume responsiveness · Passive leg raising · End-tidal carbon dioxide · Cardiac output monitoring

Introduction

Volume expansion is often the first-line treatment during acute circulatory failure. Nevertheless, fluid administration results in a significant improvement of cardiac index

(CI) in only half of cases if preload responsiveness is not previously assessed [1]. Among the different tests that have been developed for detecting preload responsiveness [2], the passive leg raising (PLR) test consists in moving the patient from the semirecumbent position to a position

in which the legs are elevated at 45° [3]. This postural change transfers blood from the leg and abdominal compartments [4] toward cardiac cavities and acts like an endogenous fluid challenge. The main advantage of the PLR test is that it remains valuable for detecting preload responsiveness in case of spontaneous breathing activity [5–11], acute respiratory distress syndrome with low tidal volume and lung compliance [12], and cardiac arrhythmias [5, 13], conditions in which the respiratory variation of stroke volume or surrogates is not valid [5, 12, 14].

Nevertheless, a disadvantage of the PLR test is that it requires a direct measure of CI. Indeed, arterial pressure alone does not allow precise assessment of PLR hemodynamic effects [15]. This is even true for the arterial pulse pressure, i.e., the value of arterial pressure which is best correlated with stroke volume [16]. This is likely due to the fact that changes in arterial pulse pressure are only roughly correlated with changes in stroke volume [17].

In this context, measuring the end-tidal carbon dioxide (EtCO₂) might be an attractive method for assessing the effects of the PLR test when no direct monitoring of CI is available. Indeed, the amount of exhaled CO₂ is proportional to CI in stable respiratory and metabolic conditions [18], and its changes have been demonstrated to reflect CI changes [19, 20]. Thus, provided that ventilation is unaltered and cell metabolism is stable, which might be true over short periods of time, EtCO₂ might allow continuous and noninvasive estimation of CI changes during PLR.

The goals of the present study were to test (1) whether the changes in EtCO₂ observed during volume expansion are able to track the simultaneous changes in CI, and (2) whether the changes in EtCO₂ during a PLR test could predict fluid responsiveness.

Patients and methods

Patients

This prospective study was approved by the Institutional Review Board of our institution. Patients were included according to an emergency procedure. Deferred informed consent was requested from the patient's surrogate as soon as possible. As he/she recovered consciousness, deferred informed consent was requested from the patient. If the patient or his/her next of kin refused consent, patient's data were not entered into analysis.

Sixty-five patients were included in the study. They were included if they were routinely monitored by a PiCCO2 device (Pulsion Medical Systems, Munich, Germany) and by a mainstream CO₂ sensor (M2741A; Philips, Böblingen, Germany, connected to the M2772A airway adapter) and if the attending physician planned to administer a volume expansion due to hemodynamic

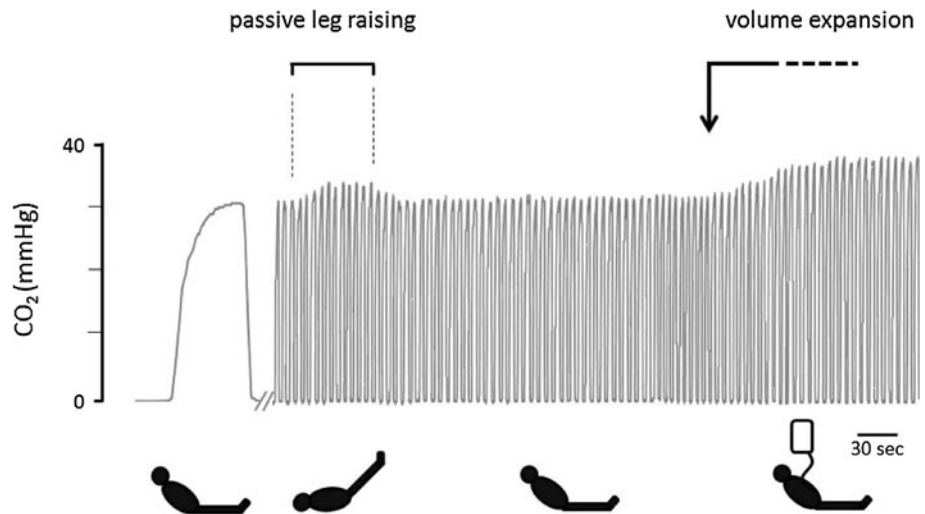
instability. Patients also had to be intubated and ventilated (Evita 4; Dräger Medical, Lübeck, Germany) in the control assisted mode with no inspiratory effort, as assessed by observing the flow curve displayed by the ventilator. Patients were excluded if they were less than 18 years old and if PLR was contraindicated (head trauma, known deep vein thrombosis of the inferior limbs, venous compression stocking).

Study design and measurements

At baseline, a first set of measurements was performed, including heart rate, systemic arterial pressure, CI (measured by transpulmonary thermodilution), and EtCO₂. A volume expansion was administered (500 mL saline over 30 min [21]). Immediately after fluid infusion, we again measured heart rate, systemic arterial pressure, CI (measured by transpulmonary thermodilution), and EtCO₂.

In 40 out of the 65 patients, a PLR test was performed before volume expansion. For this purpose, immediately after the first set of measurements, patients were transferred from the initial semirecumbent position to the PLR position, in which the legs are elevated at 45° and the trunk is in horizontal position. The postural change was performed by using the automatic motion of the bed and without changing the hip angle [4]. When the PLR had induced its maximal effect on CI, a second set of measurements was recorded, including heart rate, systemic arterial pressure, CI (measured by pulse contour analysis), and EtCO₂. The effects of PLR on CI were assessed by pulse contour analysis rather than by transpulmonary thermodilution because pulse contour analysis allows easy assessment of transient changes in CI induced by PLR. The patient was moved back to the semirecumbent position. When the hemodynamic variables reached their baseline values again and before fluid administration, we measured heart rate, systemic arterial pressure, CI (measured by transpulmonary thermodilution), and EtCO₂. This second transpulmonary thermodilution was performed after the PLR test and before volume expansion in order to very precisely measure the effects of volume expansion on CI, without taking into account the small changes that may spontaneously occur between before and after the PLR. Transpulmonary thermodilution was performed by averaging the value resulting from three successive bolus injections performed with 15 mL cold saline [22]. To assess the changes in EtCO₂, it was carefully checked by observing the EtCO₂ curve that the baseline EtCO₂ and the EtCO₂ upstroke delay did not change during PLR and volume expansion; i.e., the changes in EtCO₂ were not related to changes in inspired CO₂ or to increased airway resistance at expiration [18] [see Electronic Supplementary Material (ESM) Fig. 1].

Fig. 1 Typical recording of the exhaled carbon dioxide (CO_2) curve before and during a passive leg raising test and then before and during volume expansion. The increase in end-tidal CO_2 induced by volume expansion was preceded by a 12 % increase in end-tidal CO_2 during the passive leg raising test



Statistical analysis

Patients in whom volume expansion increased CI by more than 15 % were defined as “volume responders” and the remaining ones as “volume nonresponders.” This cutoff was justified by the fact that the least significant change (LSC) of CI measured by transpulmonary thermodilution is 12 % when three cold measurements are averaged [22].

All data except the dose of norepinephrine, and the relative changes in CI, in arterial pulse pressure, and in EtCO_2 were normally distributed (Kolmogorov–Smirnov test) and are expressed as mean \pm standard deviation (SD) or as median [25–75 % interquartile range, IQR], as appropriate. Pairwise comparisons of values between different study times were performed by paired Student’s *t* test or Wilcoxon test, as appropriate. Comparisons between volume responders and nonresponders were performed by two-tailed Student *t* test or Mann–Whitney *U* test, as appropriate. Correlations were tested by the Pearson method.

In the 40 patients in whom a PLR test was performed, the ability of the PLR-induced changes in arterial pulse pressure, in CI, and in EtCO_2 to detect volume responsiveness was tested and compared by constructing receiver-operating characteristic (ROC) curves for each variable. The areas under the ROC curves were compared by the Hanley–McNeil test [23]. Sensitivity and specificity are expressed as mean (95 % confidence interval).

We calculated the coefficient of variation of EtCO_2 as being the standard deviation divided by the mean of the measurements performed before the PLR test and before volume expansion, i.e., at times when the hemodynamic status was supposed to be similar. The precision was calculated as being two times the coefficient of variation, and the LSC as precision times $\sqrt{2}$. The LSC is the minimum change that needs to be measured by a device in order to recognize a real change. *p*-Value ≤ 0.05 was

considered statistically significant. Statistical analysis was performed using MedCalc 8.1.0.0 (Mariakerke, Belgium).

Results

Patients’ characteristics

Patients’ characteristics are detailed in Table 1. The population did not include any surgical patients. A majority suffered from septic shock (91 %) and acute respiratory distress syndrome (77 %) (Table 1). Atrial fibrillation was observed in 17 % of patients. All other patients were in sinus rhythm. All patients were sedated, but none were paralyzed. All patients were mechanically ventilated without spontaneous breathing. Fifteen percent of patients had previous chronic obstructive pulmonary disease. No patient exhibited right ventricular dilation (defined by ratio of right over left ventricular diameter >0.6) or paradoxical septal motion at echocardiography. No patient exhibited clinical signs of intraabdominal hypertension. The study was conducted over 1 year. Ten patients were excluded because of lack of cardiac index measurement.

Relationship between the changes in CI, EtCO_2 , and arterial pulse pressure induced by volume expansion

Considering all 65 episodes of volume expansion, CI increased by 12 [3–24] %, EtCO_2 by 5 [0–13] %, and arterial pulse pressure by 7 [2–22] %. CI increased by more than 15 % in 34 volume responders. In these patients, CI increased by 27 [23–42] %. Individual changes in EtCO_2 , CI, and arterial pulse pressure in responders and nonresponders are displayed in ESM Fig. 2.

Table 1 Characteristics of patients ($n = 65$)

Age (mean \pm SD, years)	60 \pm 14
Gender (male/female, no. of patients)	37/28
SAPS II (mean \pm SD)	57 \pm 19
Acute respiratory distress syndrome (no. of patients)	50
COPD (no. of patients, %)	10 (15 %)
Atrial fibrillation (no. of patients, %)	11 (17 %)
Tidal volume (mean \pm SD, mL/kg of predicted body weight)	6.4 \pm 0.8
Total PEEP (mean \pm SD, cmH ₂ O)	7 \pm 2
Arterial blood gas analysis	
pH	7.35 \pm 0.09
PaO ₂ /FiO ₂ (mean \pm SD, mmHg)	220 \pm 40
PaCO ₂ (mean \pm SD, mmHg)	34 \pm 8
EtCO ₂ (mean \pm SD, mmHg)	28 \pm 6
Lactate (mean \pm SD, mmol/L)	2.1 \pm 0.7
Left ventricular ejection fraction (mean \pm SD, %)	48 \pm 2
Type of shock (no. of patients, %)	
Septic	59 (91 %)
Hypovolemic	6 (9 %)
Patients receiving norepinephrine (no. of patients, %)	63 (97 %)
Dose of norepinephrine (median [25–75 % interquartile range], ng/kg/min)	1.8 [0.2–5.2]

COPD chronic obstructive pulmonary disease, EtCO₂ end-tidal carbon dioxide, FiO₂ inspired oxygen fraction, PaO₂ arterial oxygen partial pressure, PaCO₂ arterial carbon dioxide partial pressure, SAPS Simplified Acute Physiology Score, PEEP positive end-expiratory pressure, SD standard deviation

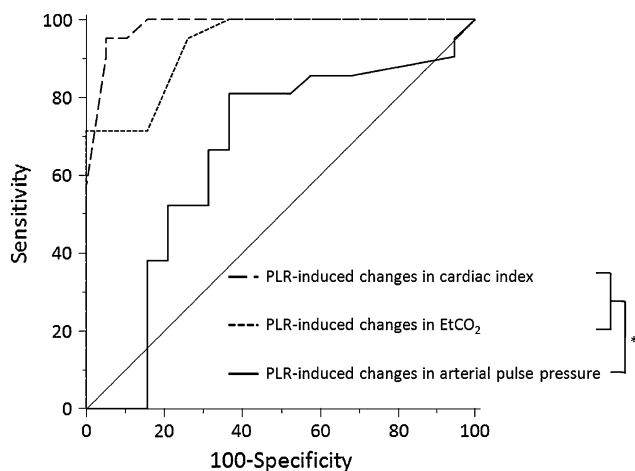


Fig. 2 Receiver-operating characteristic (ROC) curves showing the ability of the PLR-induced changes in cardiac index (CI), in end-tidal carbon dioxide (EtCO₂), and in arterial pulse pressure to predict an increase in cardiac index ≥ 15 % during the subsequent fluid administration. $n = 40$, * $p \leq 0.05$ for the comparison between areas under the curves

The correlation between absolute values of EtCO₂ and of CI was not significant, neither before nor after volume expansions. The correlation between the changes in

EtCO₂ and in CI induced by volume expansions was significant ($r^2 = 0.45$, $p \leq 0.0001$).

The correlation between absolute values of arterial pulse pressure and of CI was significant before and after volume expansions ($r^2 = 0.20$, $p \leq 0.0001$ and $r^2 = 0.15$, $p = 0.0009$, respectively). The correlation between the changes in arterial pulse pressure and in CI induced by volume expansions was significant ($r^2 = 0.31$, $p < 0.0001$).

The precision of EtCO₂ was 1.3 ± 2.1 %, and the LSC was 1.8 ± 3.0 %.

Ability of the PLR-induced changes in CI, EtCO₂, and arterial pulse pressure to predict fluid responsiveness

A typical CO₂ tracing in a responder is displayed in Fig. 1. In all patients, the maximal effects of PLR on CI and EtCO₂ were observed within 1 min. Considering the 40 patients in whom PLR was performed, the correlation between the changes in EtCO₂ and in CI induced by PLR was significant ($r^2 = 0.42$, $p < 0.0001$). The correlation between the changes in arterial pulse pressure and in CI induced by PLR was significant ($r^2 = 0.23$, $p \leq 0.0001$).

Among these 40 patients, volume expansion increased CI by more than 15 % (29 [22–45] %) in 21 volume responders. The PLR-induced changes in CI and EtCO₂ were significantly higher in the 21 volume responders than in the 19 volume nonresponders (Table 2). There was a significant correlation between the changes in CI induced by fluid administration and the changes in EtCO₂ induced by the PLR test ($r = 0.79$, $p < 0.001$). A PLR-induced increase in CI ≥ 10 % predicted a fluid-induced increase in CI ≥ 15 % with sensitivity of 95 [76–100] % and specificity of 95 [74–100] % (Table 3; Fig. 2). A PLR-induced increase in EtCO₂ ≥ 5 % predicted a fluid-induced increase in CI ≥ 15 % with sensitivity of 71 [48–89] % and specificity of 100 [82–100] % (Table 3; Fig. 2). The areas under the ROC curves constructed for the PLR-induced increase in CI and EtCO₂ were not statistically different (Table 3; Fig. 2). The area under the ROC curve for the PLR-induced changes in arterial pulse pressure was not significantly different from 0.5 (Table 3; Fig. 2).

Discussion

This study showed that EtCO₂ could be used as a non-invasive tool for assessing the response of CI to volume expansion and that the changes in EtCO₂ observed during a PLR test allowed prediction of fluid responsiveness. EtCO₂ was better than arterial pulse pressure for this purpose.

Exhaled CO₂ is determined by three factors: the production of CO₂ by cell metabolism, the pulmonary flow (i.e., cardiac output) that drives CO₂ from the periphery to the lungs, and the ability of the lung to clear the venous blood of CO₂ [24]. Thus, if two of the three factors are constant, changes in EtCO₂ might reflect changes of the third. Based upon this reasoning, previous studies showed a good correlation between EtCO₂ and cardiac output during cardiopulmonary resuscitation in animals [25] and humans [26–28]. Some studies also established that the EtCO₂ improvement during resuscitation is a prognostic indicator of resuscitated cardiac arrest [29–31] and that the changes in EtCO₂ could track changes in cardiac output during cardiopulmonary bypass [32, 33]. The present study investigated EtCO₂ as a surrogate of cardiac output for dynamic prediction of fluid responsiveness.

By showing that the changes in EtCO₂ and in CI induced by volume expansion were significantly correlated, we suggest that EtCO₂ could be used as a noninvasive tool for monitoring CI in response to preload changes, even though the correlation between the changes in EtCO₂ and CI was not perfect. Interestingly, the correlation between the absolute values of EtCO₂ and CI was not significant. This is explained by the fact that the absolute value of EtCO₂ is influenced by many other factors than CI (cell metabolism, minute ventilation, respiratory dead space), but that these factors are unchanged in the meantime of volume expansion. The amplitude of the preload-induced changes in EtCO₂ was small, but it was larger than the least significant change we determined from two EtCO₂ measurements. In other words, in patients with stable condition, EtCO₂ is a very stable variable, so that even small changes are easily detectable.

The PLR maneuver induces passive transfer of blood contained in the venous compartment of the lower limb [34] and of the abdominal compartment [4] to the heart and increases the right and left cardiac preload [35]. A number of original studies [5–11, 13] showed that the PLR test is reliable for predicting fluid responsiveness, and a meta-analysis [15] confirmed this diagnostic accuracy. By showing that PLR-induced increases in CI are able to predict the response of CI to a subsequent fluid challenge, the present study is in accordance with all these previous results. It also confirms previous observations [15] that arterial pulse pressure is less reliable than CI for assessing the hemodynamic effects of PLR. The pulse pressure is physiologically related to stroke volume [36]. Nevertheless, peripheral pulse pressure is also influenced by arterial compliance and by the pulse wave amplification phenomenon [36]. These issues of arterial compliance and pulse wave amplification phenomenon likely explain why the changes in arterial pulse pressure only roughly indicate changes in CI induced by volume expansion [17]. We confirmed in the present study that the correlation between the absolute values and fluid-induced changes in CI and in arterial pulse pressure were actually weak. As a consequence, the PLR-induced changes in arterial pulse pressure were unable to predict fluid responsiveness.

By contrast, the PLR-induced changes in EtCO₂ predicted fluid responsiveness with reliability. Our results confirm a recent study conducted in a similar population [37]. Thus, EtCO₂ could be regarded as a surrogate of CI for assessing the effects of PLR when no device is available for measuring CI directly. This can be the case in the perioperative setting or at the early phase of shock. Obviously, monitoring EtCO₂ alone might be insufficient

Table 2 Hemodynamic changes induced by preload challenges (65 fluid administrations and 40 passive leg raises)

	Before preload challenge	After preload challenge
Heart rate (mean ± SD, beats/min)		
Cases with preload responsiveness (<i>n</i> = 38)	100 ± 22	98 ± 20
Cases with preload nonresponsiveness (<i>n</i> = 67)	94 ± 18	92 ± 22
Mean arterial pressure (mean ± SD, mmHg)		
Cases with preload responsiveness (<i>n</i> = 38)	66 ± 14	75 ± 15 [#]
Cases with preload nonresponsiveness (<i>n</i> = 67)	70 ± 14*	73 ± 15
Diastolic arterial pressure (mean ± SD, mmHg)		
Cases with preload responsiveness (<i>n</i> = 38)	50 ± 10	55 ± 11 [#]
Cases with preload nonresponsiveness (<i>n</i> = 67)	53 ± 11*	54 ± 11
Arterial pulse pressure (mean ± SD, mmHg)		
Cases with preload responsiveness (<i>n</i> = 38)	52 ± 23	63 ± 27 [#]
Cases with preload nonresponsiveness (<i>n</i> = 67)	54 ± 19	58 ± 19 [#]
Cardiac index (mean ± SD, L/min/m ²)		
Cases with preload responsiveness (<i>n</i> = 38)	2.7 ± 1.2	3.6 ± 1.5 [#]
Cases with preload nonresponsiveness (<i>n</i> = 67)	3.1 ± 1.0*	3.3 ± 1.0 [#]
EtCO ₂ (mean ± SD, mmHg)		
Cases with preload responsiveness (<i>n</i> = 38)	29 ± 6	32 ± 7 [#]
Cases with preload nonresponsiveness (<i>n</i> = 67)	29 ± 6	30 ± 6 [#]

EtCO₂ end-tidal carbon dioxide, SD standard deviation

* *p* ≤ 0.05 versus cases with preload responsiveness, [#] *p* ≤ 0.05 versus “before preload challenge”

Table 3 Diagnostic ability of the passive leg raising-induced change in cardiac index, end-tidal carbon dioxide, and arterial pulse pressure to predict a fluid-induced increase in cardiac index

Variable	AUC	<i>p</i> -Value versus 0.50	Best cutoff value	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Youden index
PLR-induced changes in cardiac index	0.98 (0.88–1.00)	<0.0001	10 %	95 (76–100)	95 (74–100)	95 (76–100)	95 (74–100)	19.0 (15.7–20.9)	0.1 (0.0–0.7)	0.90
PLR-induced changes in EtCO ₂	0.93 (0.81–0.99)	<0.0001	5 %	71 (48–89)	100 (82–100)	100 (78–100)	76 (55–91)	4.5 (3.2–6.3)	0.3 (0.1–1.2)	0.71
PLR-induced changes in arterial pulse pressure	0.65 (0.49–0.80)	0.07								

AUC area under the receiver-operating characteristic curve, EtCO₂ end-tidal carbon dioxide, PLR passive leg raising *n* = 40; mean (95 % confidence interval), *p* value to the AUC

when the circulatory failure is refractory to the initial therapy and when additional hemodynamic information is mandatory [38, 39]. Additionally, it must be recalled that trends in EtCO₂ might no longer reflect trends in CI in nonventilated patients. Also, it must be underlined that EtCO₂ might help monitoring CI only over short periods. Indeed, it is plausible that, during acute circulatory failure, if the hemodynamic improvement persists, cell metabolism could shift from anaerobic to aerobic conditions, eventually leading to a change in CO₂ production.

We acknowledge some limitations to our study. First, although several devices are commercially available for monitoring EtCO₂, we only tested the mainstream technique and we cannot certify that the cutoff value reported in the present study would be identical with other EtCO₂ monitoring devices. Second, although it is conceivable that CI also changes EtCO₂ in spontaneously breathing patients provided that ventilation is regular, we did not test this hypothesis. Third, since a majority of patients were ventilated with tidal volume lower than 8 mL/kg, a condition where pulse pressure variation might not be valid for predicting fluid responsiveness [40, 41], we could not compare the predictive value of this variable

with that of the PLR-induced changes in EtCO₂. Finally, our results only apply to the specific population that we studied, i.e., patients under mechanical ventilation without spontaneous breathing activity, with normal or moderately depressed left ventricular function and normal right ventricle. Also, we could not investigate the effects of an increased intraabdominal pressure, since this condition could alter the hemodynamic effects of PLR [42].

Conclusions

The changes in EtCO₂ induced by a PLR test predicted fluid responsiveness with reliability, while the changes in arterial pulse pressure did not. EtCO₂ monitoring should thus be regarded as a noninvasive surrogate of CI during PLR when no device is available for measuring CI.

Conflicts of interest Prof. Jean-Louis Teboul and Xavier Monnet are members of the Medical Advisory Board of Pulsion Medical Systems.

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