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Changes in end-tidal CO_2 could predict fluid responsiveness in the passive leg raising test but not in the mini-fluid challenge test: A prospective and observational study☆,☆☆

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ABSTRACT

Objective: The objective is to explore the value of end-tidal carbon dioxide ($ETCO_2$) in replacing cardiac index for evaluating fluid responsiveness during the passive leg raising (PLR) test and mini-fluid challenge (mini-FC).
Methods: Patients experiencing septic shock and who were on mechanical ventilation in an intensive care unit were divided into responder and nonresponder groups according to whether their cardiac index increased by more than 10% after the FC. Before and after those tests, the changes in $ETCO_2$, central venous pressure, heart rate, mean arterial pressure, pulse pressure, and cardiac output were recorded.
Results: Of the 48 patients in the study, 34 had fluid responsiveness according to the changes in cardiac output or stroke volume. The ΔCI and $\Delta ETCO_2$ in the responder group were larger than the changes in the nonresponder group during the PLR test (1.1 ± 0.7 vs 0.2 ± 0.4 L/min per square meter, 3.0 ± 3.0 vs 0.5 ± 2.5 mm Hg; $P <$ .05) but not during mini-FC. $\Delta ETCO_2$ greater than or equal to 5% during the PLR test predicted fluid responsiveness with 93.4% specificity and 75.8% sensitivity in a receiver operating characteristic curve. The area under the curve was 0.849 (95% confidence interval, 0.739-0.930). $\Delta ETCO_2$ greater than or equal to 3% during the mini-FC predicted fluid responsiveness with 93.4% specificity and 33.3% sensitivity in a receiver operating characteristic curve, and the area under the curve was 0.781 (95% confidence interval, 0.646-0.915).
Conclusions: The changes in $ETCO_2$ may predict fluid responsiveness during the PLR test in patients with septic shock, but similar results were not found with the mini-FC.

1. Introduction

The primary treatment for shock is fluid resuscitation. The purpose of fluid resuscitation is to improve cardiac output and microvascular perfusion by adjusting the vascular volume and cardiac preload. Before fluid resuscitation, it is important to evaluate vascular volume and fluid responsiveness [1]. Fluid overload may cause pulmonary edema and hemodilution, which may decrease the oxygen supply and increase the duration of mechanical ventilation, the length of stay in an intensive care unit, and the mortality rate, especially during acute respiratory distress syndrome [2-4].

The criterion standard to evaluate whether a patient will respond to fluid is to measure changes in cardiac output or stroke volume before and after a Fluid challenge (FC) [5]. Static parameters (such as central venous pressure (CVP), global end-diastolic volume, and intrathoracic blood volume) have been shown not to be useful in predicting fluid responsiveness. Therefore, we pay more attention to dynamic parameters (stroke volume variation, pulse pressure variation, passive leg raising (PLR) test, mini-FC, and expiration hold). The PLR test consists of moving the patient from the semirecumbent position to a position in which the legs are elevated at 45°. This maneuver induces the passive transfer of blood contained in the venous compartments of the lower limbs and the abdomen to the heart, which increases the right and left cardiac preload. The test is reversible, repeatable, and easy to perform. In addition, it avoids adding extra fluid to the vascular volume and is hardly affected by arrhythmia and autonomous respiration [6-12]. In a meta-analysis, Cavallaro et al [13] agreed that the PLR test was precise and reliable for evaluating fluid responsiveness. However, in some diseases, such as intracranial hypertension and amputation, the PLR test is limited [14-16]. The important limitation is the need to monitor cardiac output, which is unachievable or inconvenient under many clinical conditions. Compared with the classic FC, a new method has been proposed for performing a FC. This method consists of administering 100 mL of colloid over 1 minute. We can observe the effects of this mini-FC on stroke volume. A mini-FC needs much less fluid, which reduces the rate of fluid overload. However, during the mini-FC, measurement of the aortic flow velocity by ultrasound is needed to judge the change in cardiac output to evaluate fluid responsiveness. This ultrasound

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monitoring is not very simple and requires a skilled technician to perform it [17,18]. Therefore, a simple and practical method to evaluate fluid responsiveness is needed. End-tidal carbon dioxide ($ETCO_2$) is determined by 3 factors: CO_2 production by cell metabolism, cardiac output, and the ability of lungs to eliminate CO_2 from venous blood [19]. Over a period, if 2 of 3 factors have not changed, then $ETCO_2$ can reflect the last factor. Some research studies have demonstrated that changes in $ETCO_2$ correlate well with changes in CO in both human and animals [20-24]. In cardiopulmonary resuscitation, $ETCO_2$ is a good indicator for the return of spontaneous circulation [25,26]. If other factors are constant during fluid resuscitation, changes in $ETCO_2$ reflect changes in CO. Therefore, if we can assessment fluid responsiveness according to changes in $ETCO_2$ rather than cardiac output, the procedure will be more meaningful and convenient to apply in a clinical setting.

In this study, we aimed to compare the relationship between $ETCO_2$ and cardiac index (CI) in the PLR test as well as the mini-FC among patients with septic shock on mechanical ventilation. Through this approach, we can judge whether the changes in $ETCO_2$ during the PLR test or mini-FC could predict fluid responsiveness.

2. Materials and methods

2.1. Patients

The Institutional Research and Ethics Committee of the Peking Union Medical College Hospital approved this study for human subjects. Written informed consent was obtained from all patients or their next of kin before their data were included in the study.

From January 2013 to August 2013, patients with septic shock in the intensive care unit of our hospital were selected for the study. The enrollment criteria included age 14 years or older, meeting 2 or more criteria for systemic inflammatory response syndrome, and either refractory hypotension or a serum lactate level of 4 mmol/L or higher. We defined refractory hypotension as a systolic blood pressure that either was less than 90 mm Hg or required vasopressor therapy to maintain 90 mm Hg even after an intravenous FC [27]. The rate of changes in the patient's heart and blood pressure was less than 10% in the 15 minutes before the research procedure, and the patients received complete respiratory support with mechanical ventilation without spontaneous breathing. The patients selected for the study should satisfy all of the enrollment criteria above unless one of the following exclusion criteria was present: contraindication of the FC (such as volume overload), contraindication of the PLR test (eg, brain trauma, brain stroke, deep vein thrombosis, lower limb, or pelvis fracture), or contraindication for using the technology in the pulse indicator to monitor continuous cardiac output (eg, intra-aortic balloon pump or extracorporeal membrane oxygenation) and intra-abdominal hypertension.

2.2. Hemodynamic monitoring

During the study, the circulation of all enrolled patients was monitored with pulse indicator continuous cardiac output (PICCO) (PulsioCath PV 2015L20; Pulsion Medical Systems, Munich, Germany). Catheters were inserted into the superior vena cava (internal jugular vein or subclavian vein) and arteria cruralis. The mean arterial pressure (MAP) was monitored from the arteria cruralis. At the end of expiration, the CVP was monitored from the superior vena cava catheter, and forceful expiration was avoided. The reference-pressure zero was located at the intersection of the fourth rib's clearance and the midaxillary line. All of the patients were mechanically ventilated with stable respiratory parameters using a respirator (Evita 4; Dra¨ger Medical, Lu¨beck, Germany). The positive end-expiratory pressure was set according to a clinical situation that has no influence on CVP, and adjustments in positive end-expiratory pressure were prohibited during the study along with adjustments in the dosage of vasoactive agents. After 3 injections of 15 mL 0.9% saline (4°C) from a catheter into the superior vena, the stroke volume index and CI can be acquired as a mean value through PICCO [28].

2.3. End-tidal carbon dioxide monitoring

End-tidal carbon dioxide was captured with the mainstream CO_2 sensor (M2741A; Philips, Boeblingen, Germany) connected to the endotracheal tube. The CO_2 sensor can transform the CO_2 concentration of the airflow into electrical signals then send those signals to the monitor, where those electrical signals are analyzed, and the parameters of CO_2 concentration is displayed.

2.4. Protocol for fluid responsiveness assessment

All of the patients received the PLR test, the mini-FC, and the FC in sequence. Before the mini-FC and FC, the circulation parameters were allowed to return to normal. In addition, before and after every step, changes in circulation parameters should be recorded. After the FC, the circulation parameters (CI) were recorded to evaluate whether the fluid responsiveness was positive.

2.5. The PLR test

The patients were kept in a semirecumbent position (~45°) for 2 minutes, and they were then transferred to a horizontal position in which their legs were elevated to 45° [3]. After 1 minute, the circulation parameters (CVP, heart rate (HR), MAP, CI, and pulse pressure [PP]) and $ETCO_2$ need to be recorded.

2.6. Mini-FC

One hundred milliliters of 0.9% saline was injected into the patient's body in 1 minute. Before and after the test, the circulation parameters and $ETCO_2$ were recorded. The decision to optimize circulation according to clinical treatment requirements was made by the physician in charge.

2.7. Fluid challenge

Five hundred milliliters of 0.9% saline was injected into the patient's body in 15 minutes. Before and after the test, the circulation parameters and $ETCO_2$ were recorded. Fluid responsiveness was defined as an increase in the CI more than 10% after the FC. The patients were classified as either volume responders (CI ≥10% after FC) or volume nonresponders (CI <10% after FC).

2.8. Statistical analysis

The statistical analyses were performed using SPSS 19.0 software (SPSS, Inc, Chicago, IL). The normal distribution data were expressed as the means ± SD and analyzed with a 2-sample t test for quantitative data or the χ^2 test for qualitative data to test differences. The abnormal distribution data were expressed as the median and analyzed with a Mann-Whitney test. Correlations between variables were analyzed with the Pearson linear regression test for normal distribution data or the Spearman rank coefficient test for abnormal distribution data. Receiver operating characteristic curves analysis was carried out to predict fluid responsiveness. A value of $P < .05$ was considered to be statistically significant.

3. Results

3.1. Basic characteristics of the included patients

A total of 50 patients with septic shock were consecutively enrolled in the study, and all of the patients finished the trial except 2 (who abandoned therapy). Among the 48 patients in the study, only 34 had