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Original Contribution

Exploring the best predictors of fluid responsiveness in patients with septic shock

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ABSTRACT

Objective: To evaluate respiratory variations in carotid and brachial peak velocity and other hemodynamic parameters to predict responsiveness to fluid challenge.
Methods: A prospective observational study was performed on mechanically ventilated patients with septic shock. Outcomes included the measurements of central venous pressure, intrathoracic blood volume index, stroke volume variation (SVV), pleth variability index(PVI), and ultrasound assessments of respiratory variations in inferior vena cava diameter (ΔIVC), carotid Doppler peak velocity (ΔCDPV), and brachial artery peak velocity (ΔVpeak brach).
Results: All patients received 200 mL normal saline challenge. There were 27 responders and 22 non-responders. Responders had higher SVV, PVI, ΔIVC, ΔCDPV, and ΔVpeak brach measurements. In addition, all these measurements had statistically significant linear correlations with changes in cardiac index (CI).When responders were defined by ΔCI ≥ 10%, receiver operating characteristics (ROC) curve analysis showed that fluid responsiveness could be predicted:11.5% optimal cut-off 1evels of SVV with sensitivity of 75% and specificity of 85%, 15.5% optimal cut-off 1evels of PVI with sensitivity of 65% and specificity of 80%, 20.5% optimal cut-off 1evels of ΔIVC with sensitivity of 67% and specificity of 77%, 13% optimal cut-off 1evels of ΔCDPV with sensitivity of 78%% and specificity of 90%, 11.7% optimal cut-off 1evels of ΔVpeak brach with sensitivity of 70% and specificity of 80%.
Conclusion: Ultrasound assessment of ΔIVC and ΔVpeak brach, especially ΔCDPV, could predict fluid responsiveness and might be recommended as a continuous and noninvasive method to monitor functional hemodynamic parameter in mechanically ventilated patients with septic shock.

1. Introduction

Septic shock is a serious infectious condition characterized by low blood pressure and multiple organ damage. One of the traditional recommendations is to administer intravenous fluids as the first step to improve blood pressure [1,2]. However, studies have shown that not every patient benefits from aggressive intravenous hydration [3,4]. Only about 40% of hypotensive patients with sepsis respond to fluid infusion with improvement in blood pressure and outcomes [5,6]. Those who do not respond to fluid infusion are liable to develop high intravascular pressure, pulmonary edema, heart failure with a high associated mortality [7-9]. Therefore, it is crucial to develop a hemodynamically-guided approach to evaluate volume status and to identify patients who are likely to benefit from fluid administration.

Previous studies have shown that certain parameters may correlate with volume status. The traditional static parameters, such as central venous pressure (CVP), pulmonary wedge pressure, and intrathoracic blood volume index (ITBVI), have been shown not to correlate with patient volume status [10,11]. Hemodynamic parameters, such as stroke volume variation (SVV) and pleth variability index (PVI) may better predict fluid responsiveness. However, assessments of these parameters require invasive procedures and special monitoring equipment, which limits their clinical application [12].

In recent years, ultrasound has been proposed as a tool to help guide fluid resuscitation [13,14]. According to the Frank-Starling curve, when patients are in the low volume status, the cardiac preload is low and the curve is in the rising phase,therefore intrathoracic pressure fluctuations by breathing could have a greater impact on cardiac stroke volume(SV) [15,16]. The variation of SV may be assessed by variation of arterial blood peak velocity on the Doppler ultrasound. At last, it leads the higher variation of SV and arterial blood peak velocity. Studies have shown that respiratory variation in aortic blood peak velocity had high sensitivity and specificity to predict fluid responsiveness [17-19]. However, measurements of aortic blood flow velocity require transesophageal ultrasound which is an invasive procedure. Measurements of femoral artery blood flow are frequently affected by changes in intra-abdominal pressure. Measures of carotid or brachial artery flow were

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Table 1
Baseline characteristics of study participants

	Responder group ($N = 27$)	Non-responder group ($N = 22$)
Age, year, mean ± SD	55.7 ± 12.6	55.0 ± 12.8
Gender, male/female, N	19/8	14/8
Body mass index, kg/m^2, mean ± SD	24.6 ± 9.3	25.3 ± 9.5
APACHE II score, mean ± SD	26.5 ± 10.0	27.2 ± 10.5
SOFA score, mean ± SD	18.3 ± 7.2	18.6 ± 7.5
Sources of infection, N (%)		
Respiratory tract	18 (66.7%)	15 (68.2%)
Urinary tract	4 (14.8%)	3 (13.6%)
Gastrointestinal	2 (7.4%)	1 (4.5%)
Hematogenous	1 (3.7%)	1 (4.5%)
Others	2 (7.4%)	2 (9.1%)

SOFA: Sequential Organ Failure Assessment.
APACHE: Acute Physiology and Chronic Health Evaluation.

recently shown to predict fluid responsiveness [18-21]. Both these peripheral arteries are relatively superficial large vessels which can provide easy ultrasound evaluation and high-quality images. However, assessment of respiratory variation in artery peak velocity in these two arteries in ventilated patients with septic shock has not been studied.

In the current study, we measured the respiratory variation in arterial blood peak velocity in carotid and brachial arteries and compared their use against that of other static and hemodynamic parameters for predicting fluid responsiveness in ventilated patients with septic shock. Clinical application of these measures is discussed.

2. Materials and methods

2.1. Study design and patient selection

A prospective observation study was performed in the Intensive Care Unit in our hospital between January 2012 and December 2015. Study protocol was approved by the Institutional Ethics Committee. Written informed consent was obtained from every patient's health care proxy.

Inclusion criteria were: 1) age ≥ 18 years; 2) patients who met the diagnostic criteria for septic shock, which was defined as systolic blood pressure (SBP) <90 mmHg, or mean arterial pressure (MAP) <70 mmHg, or SBP decreases 40 mmHg or less than two standard deviations below normal for age in the absence of other causes of hypotension [1]; 3) mechanical ventilation was prescribed and administered by clinical physicians. Ventilator settings followed the hospital written protocols. Exclusion criteria were: 1) any contraindication to fluid resuscitation, such as congestive heart failure or evidence of fluid overload; 2) pregnant women; 3) patients with neurogenic shock, cerebrovascular accident, or traumatic brain injury; 4) conditions which could affect abdominal ultrasound, such as abdominal compartment syndrome, flatulence, and patients who had undergone upper abdominal surgery; 5) arrhythmia; 6) peripheral vascular disease or stenosis.

2.2. Study protocol and outcome measurements

Patients' baseline characteristics, including gender, age, body mass index, source of infection, SOFA (Sequential Organ Failure Assessment) and APACHE (Acute Physiology and Chronic Health Evaluation) scores, were recorded.

All patients received fluid challenge with a rapid infusion of 200 mL of normal saline administered via a central venous line within 10 min [22]. CO was monitored by PiCCO (PiCCO Plus, Pulsion Medical Systems, Munich, Germany).

Cardiac index was calculated as(cardiac output)/(body surface area). Patients who showed an increase in cardiac index of ≥10% were categorized as responders; those who showed <10% increase in cardiac index were categorized as non-responders group.

Central venous pressure (CVP) was monitored via a central venous catheter (ARROW, Arrow international, INC. New Jersey, USA); intrathoracic blood volume index (ITBVI) and stroke volume variation (SVV) were assessed using a PiCCO system. Pleth variability index (PVI) was monitored by pleth variability index machine (Masimo, Radical-7, USA) and was calculated from respiratory variations in pulse oximeter.

Inferior vena cava was evaluated by a subcostal long axis view with a 4 MHz frequency ultrasound probe (Sonosite, WA, USA). A time-motion record of the IVC diameter was generated by M-mode imaging at 2 cm from the right atrium. Maximum and minimum diameters of the IVC were recorded within one respiratory cycle and were repeated three times. Respiratory variation in inferior vena cava diameter (ΔIVC) was calculated as $\Delta IVC = (IVC_{max} - IVC_{min}) / IVC_{min} \times 100\%$.

Carotid artery was identified by a 12 MHz frequency ultrasound probe (Sonosite, WA, USA) transversely placed at the inferolateral border of the thyroid cartilage. Then, 2 cm below the carotid artery bifurcation, probe was turned 90 degrees to show longitudinal view of the carotid artery. Pulsed Doppler analysis was performed at the center of the vessel, with an angulation of no >60 degrees. Maximum and minimum peak systolic velocities were recorded in a single respiratory cycle; measurements were repeated three times. Respiratory variation in carotid Doppler peak velocity (ΔCDPV) was calculated as $2 \times (CDPV_{max} - CDPV_{min}) / (CDPV_{max} + CDPV_{min}) \times 100\%$.

Brachial artery was examined with pulsed Doppler analysis (Sonosite, WA, USA) at the elbow fossa when the patients were in supine positions. Maximum and minimum peak velocity in a single respiratory cycle was recorded and repeated three times. Respiratory variations in brachial artery peak velocity (ΔVpeakbrach) was calculated as $({}_{max}Vpeak\ brach - {}_{min}Vpeak\ brach) / [({}_{max}Vpeak\ brach + {}_{min}Vpeak\ brach) / 2] \times 100\%$.

All these hemodynamic parameters were measured by certified ultrasound technicians before and after fluid challenge.

All patients were administered mechanical ventilation (VT 8–10 mL/kg, PEEP 5–12 cmH_2O), antibiotics, vasoactive agents, sedative and analgesic medications, as determined by the treating physicians according to each patient's situation.

2.3. Statistical analysis

Numerical data are presented as mean ± standard deviation, when appropriate, and analyzed using student *t*-test. Correlations were assessed on Pearson correlation analysis. Predictive value of the measured parameters for volume resuscitation was evaluated on receiver operating characteristic (ROC) curve analysis, and presented as area

Table 2
Comparison of hemodynamic parameters between responder and non-responder groups

Hemodynamic parameters	Before fluid challenge		After fluid challenge	
	Responder group	Non-responder group	Responder group	Non-responder group
CVP (mmHg)	7.3 ± 3.2	8.0 ± 3.6	9.8 ± 3.8	10.6 ± 3.9
ITBVI (mL/m^2)	880.2 ± 185.3	841.2 ± 190.0	932.3 ± 210.8	928.3 ± 202.5
SVV (%)	13.5 ± 2.3	9.0 ± 3.1*	11.0 ± 4.0	8.9 ± 3.0
PVI (%)	16.3 ± 3.1	12.5 ± 3.5*	15.9 ± 3.3	11.8 ± 3.0
ΔIVC (%)	23.3 ± 5.2	16.5 ± 3.8*	16.3 ± 4.2	14.2 ± 2.3
ΔCDPV (%)	15.2 ± 3.2	10.2 ± 2.5*	12.0 ± 2.5	10.0 ± 3.0
ΔVpeak brach (%)	14.6 ± 3.4	9.5 ± 2.5*	11.5 ± 2.8	8.8 ± 2.1

Data expressed as mean ± standard deviation.
CVP, central venous pressure; ITBVI, intrathoracic blood volume index; SVV, stroke volume variation; PVI, pleth variability index; ΔIVC, respiratory variation in inferior vena cava diameter; ΔCDPV, respiratory variation in carotid Doppler peak velocity; ΔVpeak brach, respiratory variations in brachial artery peak velocity.
* $P < 0.05$.