

Original Article

Correlation between global end-diastolic volume index and central venous pressure during fluid resuscitation in patients with severe sepsis

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Abstract: Objective: To explore the correlation between the hemodynamics monitoring indexes of global end-diastolic volume index (GEDVI) and central venous pressure (CVP) indicated by pulse induced continuous cardiac output (PiCCO) in severe sepsis patients during fluid resuscitation, as well as its clinical application value. Methods: Twenty patients in our hospital who met the diagnostic criteria of sepsis were recruited for retrospective analysis. All the patients were treated with fluid resuscitation, which was strictly in accordance with the *International Guidelines for Management of Sepsis and Septic Shock: 2016*. The GEDVI and CVP hemodynamic parameters were measured and recorded at 0, 6, 12, 24, 48 and 72 h during the treatment; their correlations at different time points were assessed by single-factor linear analysis; the correlations between different CVP ranges and GEDVI after treated for 6 h were analyzed by rank test. Results: There was correlation between GEDVI and CVP after patients being treated for 6 h ($r=-0.712$, $P=0.021$), but no significant correlation between the two was found after them being treated for 12, 24, 48 and 72 h ($r=-0.243$, $r=-0.167$, $r=-0.106$, $r=-0.138$ respectively, all $P>0.05$). Hierarchical comparison showed that when the CVP was at ranges of 0-8 mmHg or greater than 12 mmHg, it has no correlation with the GEVDI ($r=-0.534$, -0.075 respectively, both $P>0.05$); while the CVP was within 8-12 mmHg, there was an obvious negative correlation between GEDVI and CVP ($r=-0.889$, $P=0.001$). Conclusion: GEDVI can accurately reflect the cardiac preload of patients with sepsis, while the CVP, as a severe sepsis patients' therapeutic index during fluid resuscitation, cannot truly reflect the volume status of patients.

Keywords: Sepsis, global end-diastolic volume index, central venous pressure, correlation analysis, fluid resuscitation

Introduction

Sepsis and septic shock are common causes of death in critical care medicine; their incidences increased year by year recently [1]. Fluid resuscitation is one of the important treatment methods for sepsis, but it is easy to develop congestive heart failure, therefore, monitoring the cardiac preload in patients with septic shock effectively and timely has critical clinical significance in guiding the fluid resuscitation [2]. At present, the traditional clinical therapeutic index for the guidance of fluid resuscitation is still the central venous pressure (CVP), but with the development of pulse induced continuous cardiac output (PiCCO) monitoring technique, many scholars have proposed that CVP can't objectively reflect the status of the effective circulating blood volume and the cardiac

volume load. They thought that the global end-diastolic volume index (GEDVI), monitored by PiCCO, could reflect the cardiac preload more accurate [3]. However, until now, the study of volume treatment guided by GEDVI rather than CVP in sepsis patients is rare. So, in this study, correlation analysis between GEDVI and CVP in sepsis patients was conducted to assess the clinical value of GEDVI-guided volume treatment of sepsis, in the hope of providing evidence for more reliable clinical test indexes in sepsis treatment.

Material and methods

Subjects

A total of 20 patients who met the diagnostic criteria of sepsis and treated in our hospital from April 2013 to April 2017 were enrolled in

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the study. There were 10 males and 10 females with an average age of 64.3 ± 11.7 years. The written informed consents were obtained from all patients/their families, and the study was approved by the Ethics Committee of our hospital.

Inclusion criteria: The sepsis diagnosis was in accordance with the *International Guidelines for Management of Sepsis and Septic Shock: 2016* [4]; patients with acute physiology and chronic health evaluation II score ≥ 18 points; patients who accepted PiCCO monitoring and with complete clinical material. **Exclusion criteria:** Patients with diseases that would affect the monitoring of PiCCO, such as massive pulmonary embolism, severe arrhythmia, intracardiac shunt, severe valvular heart disease and acute coronary syndrome; patients with condition that would affect the accuracy of CVP, including pneumothorax, intra-abdominal hypertension, high positive end-expiratory pressure and so on; patients combined with hemorrhagic shock and cardiogenic shock, etc.

Therapeutic methods

The fluid resuscitation indications and fluid resuscitation end point were in accordance with the *International Guidelines for Management of Sepsis and Septic Shock: 2016*; all patients in this study accepted early fluid resuscitation; fluid infusion was performed according to the CVP and GEDVI. The CVP were recorded at 0 h, 6 h, 12 h, 24 h, 48 h and 72 h respectively during the treatment; the value of GEDVI at each corresponding time point was obtained by PiCCO monitor; meanwhile, all patients were given constant electrocardiograph monitoring. The endpoint of fluid resuscitation was maintaining the CVP within 8-12 mmHg and GEDVI within 650-800 ml/m²; All patients were in horizontal position, and the application of vasoactive drugs and anti-infective agents were performed according to the requirements in *International Guidelines for Management of Sepsis and Septic Shock: 2016*.

PiCCO monitoring

The PiCCO monitor (PULSION Medical Systems) was applied. Patients were in horizontal position; the right subclavian or internal jugular venous dual-lumen catheter was placed; then femoral artery puncture was performed; a catheter with thermistor wire on the tip was placed.

The PiCCO monitor connected the deep vein catheter, the femoral artery catheter and the PiCCO module. While monitoring, PiCCO module would calculate the body surface area and the injection volume of ice-cold saline through the general information of patients; normal saline at 0-4°C was injected within 5 s via central venous catheter, 3 times in a row, calculating the mean value of three test results. The techniques of transpulmonary thermal dilution and arterial pulse profile analysis were used for thermal dilution curve detection; then the GEDVI value was calculated [5].

CVP monitoring

Patients were in horizontal position; right cervical or subclavian vein puncture was performed, and a double central venous catheter was placed. The intersection point of the right midaxillary line and the fourth intercostal was regarded as the zero point; the CVP value was read at the end-expiratory of the whole respiratory cycle [6].

Statistical analysis

SPSS 19.0 was used for statistical analysis. The measurement data were expressed as mean \pm standard deviation ($\bar{x} \pm sd$); the correlation between GEDVI and CVP at different time points was evaluated by Pearson linear correlation analysis; the correlation between different CVP ranges and GEDVI was analyzed by rank test. All statistical analyses were based on the inspection level of $\alpha=0.05$.

Results

Correlation analysis between GEDVI and CVP at different time points

The results of Pearson correlation analysis showed that CVP level was correlated with GEDVI level after treated for 6 h ($r=-0.712$, $P=0.021$). There was no significant correlation between CVP and GEDVI after patients being treated for 12 h, 24 h, 48 h and 72 h ($r=-0.243$, $r=-0.167$, $r=-0.106$ and $r=-0.138$ respectively, all $P>0.05$). See **Table 1**.

Hierarchical comparison between CVP and GEDVI

The rank test results of CVP and GEDVI levels after treated for 6 h showed that when CVP was

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Table 1. Correlation analysis between GEDVI and CVP at different time points

Time points	CVP (mmHg)	GEDVI (ml/m ²)	r value	P value
0 h	7.2±2.2	709.4±12.4	-0.325	0.078
6 h	11.5±3.1	725.0±14.1	-0.712	0.021
12 h	15.2±2.6	731.4±11.9	-0.243	0.089
24 h	8.2±2.5	719.3±10.5	-0.167	0.154
48 h	7.7±1.7	694.2±8.2	-0.106	0.218
72 h	13.1±2.7	754.8±9.3	-0.138	0.177

Note: GEDVI, global end-diastolic volume index; CVP, central venous pressure.

Table 2. Comparison of rank test results between CVP and GEDVI

Stratification	CVP (mmHg)	GEDVI (ml/m ²)	r value	P value
All patients	7.9±3.3	729.4±13.4	-0.170	0.165
0 mmHg<CVP<8 mmHg	6.5±2.4	715.0±8.1	-0.534	0.056
8 mmHg≤CVP≤12 mmHg	11.7±2.6	727.8±10.9	-0.889	0.001
CVP>12 mmHg	14.8±3.5	746.6±14.6	-0.075	0.289

Note: GEDVI, global end-diastolic volume index; CVP, central venous pressure.

at ranges of 0-8 mmHg or greater than 12 mmHg, it has no correlation with GEDVI ($r=-0.534$, $r=-0.075$ respectively, both $P>0.05$); while CVP was 8-12 mmHg, CVP and GEDVI had a significantly negative correlation ($r=-0.889$, $P=0.001$), see **Table 2**.

Discussion

One of the important circulation supports in the treatment of sepsis is to offer appropriate liquid resuscitation, through which the circulating blood volume can be effectively increased and the tissue perfusion can be improved [2]. However, too much or too quick liquid infusion will further aggravate the cardiac preload, tissue edema and capillary leak, resulting in pulmonary edema, heart failure, brain edema and other complications, and even increasing the fatality rate [7]. Therefore, in the clinical practice of critical care medicine, there is a need for an accurate and sensitive hemodynamics monitoring indicator to guide fluid resuscitation [8].

Previously, the pressure of the junction of vena cava and right atrium (the CVP value) was often used to indirectly reflect the cardiac preload in clinic. However, this method had a disadvantage of poor accuracy and it was easily interfered by mechanical ventilation, position of catheter tip, cardiac compliance, application of vasoactive drugs, thrombosis and other factors

[9-11]. Consequently, many scholars have questioned the guiding significance and clinical value of CVP in the treatment of sepsis [12]. In recent years, clinical studies have confirmed that PICCO technology applied to monitor GEDVI indicator can directly reflect the cardiac preload and the status of effective circulating blood volume, accurately know the patients' fluid distribution and extravascular lung water, and detect pulmonary edema in the early stage; meanwhile, this method was not affected by catheter position, mechanical ventilation, myocardial contractility and other factors [13-16]. As

a result, some clinical researchers put forward to use GEDVI as an indicator to guide fluid resuscitation in the treatment of sepsis patients, but this viewpoint was still controversial. Therefore, this study retrospectively analyzed the clinical data of sepsis patients admitted to our hospital in order to evaluate the correlation and accuracy of CVP and GEDVI indicators during the fluid resuscitation treatment in sepsis patients.

The results of this study showed that CVP value had a correlation with GEDVI value in the early 6 h of liquid resuscitation, indicating that CVP could be used as a reliable index for fluid resuscitation in the early 6 h treatment of sepsis patients. However, it was noteworthy that there was no correlation between CVP and GEDVI levels at the beginning of the treatment and other time points after 6 h, which was indicating that CVP value could hardly accurately reflect the effective capacity status of severe sepsis patients after treated for 6 h. The reasons might be the significant increase of vascular permeability, the decrease of vascular tension, the suppression of myocardial contractility and other pathological changes in the early stages of sepsis, which would lead less blood flow back to heart, and accordingly, less cardiac output [17]. When patients received timely fluid resuscitation in the early stage, with the gradually increasing of effective circulating

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blood volume, CVP also increased gradually; accordingly, cardiac preload and cardiac output were improved little by little. So, there was a certain correlation between the changes of CVP and GEDVI values in sepsis patients treated within 6 hours, which was consistent with the existing research reports [18].

However, pathophysiology studies confirmed that the pressure and volume showed a curvilinear relationship rather than a linear relationship in cardiac function curve; after the early stage of the treatment, initial recovery goal had achieved in sepsis patients, whose cardiac function was in the plateau phase, and a small increase of circulation volume would lead to a significant increase of CVP; therefore, there was no correlation between the two at this moment [19, 20]. Namely, CVP could not accurately reflect effective circulation volume status of body after 6 h fluid resuscitation in sepsis patients. This illustrated that CVP only had good monitoring values in the early treatment, and it could not objectively reflect the effective blood volume status in the later treatment.

This study also showed no significant linear correlation between CVP and GEDVI in the evaluation of all patients. Further stratification analysis showed that there was a linear correlation between CVP and GEDVI in the condition of $8 \text{ mmHg} \leq \text{CVP} \leq 12 \text{ mmHg}$ (defined by the *Guidelines*), which indicated that in the above range, adjusting fluid intake and output in accordance with GEDVI had the same clinical value as adjusting CVP index in the evaluation of effective circulating blood volume. Nevertheless, there was no significant linear correlation between CVP and GEDVI when CVP at ranges of 0-8 mmHg and greater than 12 mmHg. When the CVP value was more than 12 mmHg, it suggested that sepsis patients would no longer make effectively response to the volume; when CVP value was between 0 and 8 mmHg, it indicated that patients needed fluid resuscitation, and CVP and GEDVI appeared a weak linear correlation; those showed that the two indexes did not have similar assessment value, which was consistent with the research results of Wang et al. [6].

In conclusion, compared with CVP, GEDVI can more accurately reflect the cardiac volume load status of sepsis patients for the whole course, and there is no significant linear dependence

between the two. CVP cannot accurately assess the effective circulating blood volume, and cannot serve as a reliable indicator for guiding fluid resuscitation. Meanwhile, there was a linear correlation between CVP and GEDVI in the condition of $8 \text{ mmHg} \leq \text{CVP} \leq 12 \text{ mmHg}$. However, for this study used retrospective method and the number of selected cases was relatively small, there were some limitations. Hence, the correlation between CVP and GEDVI in the treatment of sepsis still requires prospective, multicenter, randomized, controlled clinical trials to verify.

Disclosure of conflict of interest

None.

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References

- [1] Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, Vincent JL, Townsend S, Lemeshow S and Dellinger RP. Outcomes of the surviving sepsis campaign in intensive care units in the USA and Europe: a prospective cohort study. *Lancet Infect Dis* 2012; 12: 919-924.
- [2] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL and Moreno R. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Intensive Care Med* 2013; 39: 165-228.
- [3] Ma S, Zhang RM, Wang SF, Zhao ML, Wang L and Zhang Y. Effect of global end diastolic volume index guidance fluid resuscitation in elderly patients with septic shock. *Chinese Critical Care Medicine* 2017; 29: 486-490.
- [4] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerf B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellingham GJ, Bernard GR, Chiche JD, Cooper-Smith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones

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- AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL and Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017; 43: 304-377.
- [5] Liu N and Gu Q. Clinical study of global end-diastolic volume as an indicator of cardiac preload in septic shock patients. *Chinese Journal of Emergency Medicine* 2008; 17: 137-140.
- [6] Wang JB, Wang H, Chen QK, Cen ZR, Tang Y, Cai L, Liu ZG and Chang P. Role of central venous pressure, global end diastolic volume index and extralvascular lung water index in evaluating fluid resuscitation in patients with septic shock. *Journal of Southern Medical University* 2014; 34: 1334-1336.
- [7] Zhao J and Wang G. Inferior vena cava collapsibility index is a valuable and non-invasive index for elevated general heart end-diastolic volume index estimation in septic shock patients. *Med Sci Monit* 2016; 22: 3843-3848.
- [8] Trof RJ, Danad I and Groeneveld AJ. Global end-diastolic volume increases to maintain fluid responsiveness in sepsis-induced systolic dysfunction. *BMC Anesthesiol* 2013; 13: 12.
- [9] Garg M, Sen J, Goyal S and Chaudhry D. Comparative evaluation of central venous pressure and sonographic inferior vena cava variability in assessing fluid responsiveness in septic shock. *Indian J Crit Care Med* 2016; 20: 708-713.
- [10] Cherpanath TG, Geerts BF, Maas JJ, de Wilde RB, Groeneveld AB and Jansen JR. Ventilator-induced central venous pressure variation can predict fluid responsiveness in post-operative cardiac surgery patients. *Acta Anaesthesiol Scand* 2016; 60: 1395-1403.
- [11] Beitz A, Barbara H, Mair S, Henschel B, Lahmer T, Rasch S, Schmid R and Huber W. Consistency of cardiac function index and global ejection fraction with global end-diastolic volume in patients with femoral central venous access for transpulmonary thermodilution: a prospective observational study. *J Clin Monit Comput* 2017; 31: 599-605.
- [12] Kapoor PM, Bhardwaj V, Sharma A and Kiran U. Global end-diastolic volume an emerging preload marker vis-a-vis other markers- Have we reached our goal? *Ann Card Anaesth* 2016; 19: 699-704.
- [13] Sasai T, Tokioka H, Fukushima T, Mikane T, Oku S, Iwasaki E, Ishii M, Mieda H, Ishikawa T and Minami E. Reliability of central venous pressure to assess left ventricular preload for fluid resuscitation in patients with septic shock. *J Intensive Care* 2014; 2: 58.
- [14] Proulx F, Lemson J, Choker G and Tibby SM. Hemodynamic monitoring by transpulmonary thermodilution and pulse contour analysis in critically ill children. *Pediatr Crit Care Med* 2011; 12: 459-466.
- [15] Kaneko T, Kawamura Y, Maekawa T, Tagami T, Nakamura T, Saito N, Kitazawa Y, Ishikura H, Sugita M, Okuchi K, Rinka H, Watanabe A, Kase Y, Kushimoto S, Izumino H, Kanemura T, Yoshikawa K, Takahashi H, Irahara T, Sakamoto T, Kuroki Y, Taira Y, Seo R, Yamaguchi J and Takatori M. Global end-diastolic volume is an important contributor to increased extravascular lung water in patients with acute lung injury and acuterespiratory distress syndrome: a multicenter observational study. *J Intensive Care* 2014; 2: 25.
- [16] Barbara H, Mair S, Beitz A, Henschel B, Schmid RM and Huber W. Pulmonary vascular permeability index and global end-diastolic volume: are the data consistent in patients with femoral venous access for transpulmonary thermodilution: a prospective observational study. *BMC Anesthesiol* 2014; 14: 81.
- [17] Grindheim G, Eidet J and Bentsen G. Transpulmonary thermodilution (PiCCO) measurements in children without cardiopulmonary dysfunction: large interindividual variation and conflicting reference values. *Paediatr Anaesth* 2016; 26: 418-424.
- [18] Huber W, Mair S, Gotz SQ, Tschirdewahn J, Frank J, Hollthaler J, Phillip V, Schmid RM and Saugel B. A systematic database-derived approach to improve indexation of transpulmonary thermodilution-derived global end-diastolic volume. *J Clin Monit Comput* 2017; 31: 143-151.
- [19] Mallat J, Lemyze M, Salleron J, Benzidi Y, Barrailler S, Pepy F, Gasan G, Tronchon L and Thevenin D. Mathematical coupling of data between global-end diastolic volume index and cardiac index calculated by the PiCCO device: myth or reality? *Minerva Anesthesiol* 2014; 80: 996-1004.
- [20] Broch O, Renner J, Gruenewald M, Meybohm P, Höcker J, Schöttler J, Steinfath M and Bein B. Variation of left ventricular outflow tract velocity and global end-diastolic volume index reliably predict fluid responsiveness in cardiac surgery patients. *J Crit Care* 2012; 27: 325, e7-13.