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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

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: This study aimed to investigate the relationship between the inferior vena cava respirophasic variation (IVC collapsibility index [IVCCI]) and the general heart end-diastolic volume index (GEDVI). By determining the above relationship, we could evaluate the utility of IVCCI as an indicator.

Material/Methods: Forty-two septic patients were finally enrolled in this study. The inferior vena cava's diameter was measured with the largest at the end of expiration (IVC3) and with the smallest at the end of inspiration (IVCi) on the ultrasound (IVCCI=[(IVCD e – IVCD i)/IVCD e] ×100%). The central venous pressure (CVP), cardiac index (CI), and GEDVI were also measured at least 3 times. After fluid resuscitation therapy, the patients with a CI increase induced by more than 15% and less than 15% were classified as the positive response group (PRG) and the negative response group (NRG), respectively.

Results: After treatment, the average levels of CVP, CI, and GEDVI were significantly higher ($P<0.01$) in both groups, whereas the IVCCI was reduced. CVP, CI, and GEDVI were negatively correlated with IVCCI in both groups. The correlation coefficient between IVCCI and GEDVI was the greatest (correlation coefficient in the PRG group was 0.889 and in the NRG group it was 0.672). The ROC curve analysis indicated that IVCCI illustrated the best area under the curve, with a sensitivity of 100% and specificity of 100%, and a cut-off value of 12.9% to predict GEDVI <600 ml/m^2 in the PRG group.

Conclusions: IVCCI was a good predictor of low-volume state. The IVCCI appears to be a valuable and non-invasive index for the estimation of elevated GEDVI during fluid resuscitation in septic shock patients.

MeSH Keywords: Amniotic Fluid • Heart • Vena Cava, Inferior

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Background

Low blood volume can result in circulatory failure in patients with septic shock. Deficient capacity can cause tissue hypoperfusion, microcirculation dysfunction, and vital organ failure. However, excess liquid expansion may also cause cardiac insufficiency, pulmonary edema, and other adverse clinical consequences [1]. Although it is essential to optimize cardiac preload immediately to maintain tissue perfusion in patients with severe sepsis, it is difficult to appropriately evaluate the status of cardiac preload in patients during the early phase of severe sepsis.

However, monitoring vital signs and blood biochemical indices for predicting capacity in septic patients is not precise because they are influenced by various clinical conditions [2]. It also takes too long to receive the results. Measurements of central venous pressure (CVP) and pulmonary capillary wedge pressure (PAWP) through central venous and pulmonary artery catheters are based on pressure and affected by many factors, such as cardiovascular adaptability, chest cavity pressure, valvular regurgitation, and intra-abdominal pressure [3].

In recent years, more reliable parameter for cardiac preload has been elucidated and use of minimally invasive methods to evaluate capacity in septic patients has become especially popular. These methods include pulse indicates continuous cardiac output (PiCCO) to measure general end-diastolic volume index (GEDVI) and ultrasound to measure the degree of variation of the vena cava [4]. Global end-diastolic volume index (GEDVI), a static volumetric parameter, is considered to be better than CVP or PAWP at determining cardiac preload in patients with septic shock [5]. Evidence from clinical trials of septic patients confirms that PiCCO measurements can guide capacity treatment and markedly reduce mortality [6,7]. However, in clinical practice, it is hard to immediately do the measurement of GEDVI, which necessitates an expansive PiCCO device and a specific monitor during the early phase of sepsis. Moreover, 3 recent high-quality controlled trials reported that invasive hemodynamic monitoring is not associated with better outcome at the early phase of septic shock [8–10]. Bedside ultrasound is a non-invasive and immediate hemodynamic evaluation, and can identify capacity status just like PiCCO, and it is more convenient for clinicians to use in evaluating response to fluid resuscitation. Therefore, we attempted to evaluate inferior vena cava collapsibility index (IVCCI) as an indicator for capacity. Because there are no studies correlating IVCCI and PiCCO monitoring index, we monitored the change in IVCCI before and after fluid treatment in septic shock patients. We also investigated the relevance of qualitative and quantitative measurements of IVCCI and GEDVI.

Table 1. General data of all patients.

Content	NRG (n=10)	PRG (n=32)
Sex (Male/Female)	6/4	16/16
Age (year)	51±11	47±8
Left ventricular ejection fraction (%)	57±12	59±14
Renal function (μmol/L)	108±12	98±14
Urine output (L/24 h)	1.1±0.4	1.2±0.6
Lactate (mmol/L)	5.4±0.8	4.7±1.3
ApachII score	19±4	21±6

Data given as mean ±SD.

Material and Methods

Demographicdata

Use of human data in this observational clinical study was first approved by the local ethics committee of our hospital on 23 September 2013. All of the patients provided informed consent. In total, 45 patients were admitted to the intensive care unit with septic shock between October 2013 and March 2014 according to the following definition [3]: (A) evidence of clinical infection; (B) presence of systemic inflammatory response syndrome; (C) systolic blood pressure lower than 90 mm Hg or decreased more than 40 mm Hg from the original values for at least 1 h, or depending on vasopressor infusion to maintain blood pressure; (D) tissue hypoperfusion phenomenon, such as decreased urine output (<30 ml/h) for more than 1 h. All the patients were enrolled with an onset of sepsis syndrome ≤24 h. Three patients were excluded from analysis for not meeting study criteria. Exclusion criteria were: combination of portal hypertension and severe peripheral vascular disease; cardiac disease, including valvular heart disease and arrhythmia; and respiratory disease, including ARDS, pneumothorax, and COPD. Obese or postoperative patients were also excluded because of the difficulty in measuring inferior vena cava diameter. The general data of 42 patients are included in Table 1.

Administration of PiCCO

A central venous catheter (Arrow, Asheboro, NC, USA) was inserted in the subclavian vein, and was confirmed to be placed in the superior vena cava by bedside echo exam for analysis. The zero point was corrected and the CVP read. The PiCCO catheter (4F, PULSION, Feldkirchen, Germany) was placed via the femoral artery prior to connecting the monitor. The temperature probe was connected to the subclavian vein catheter. After the monitor was ready, mean arterial pressure (MAP), CI, GEDVI, and ITBVI were recorded. During measurement, 20

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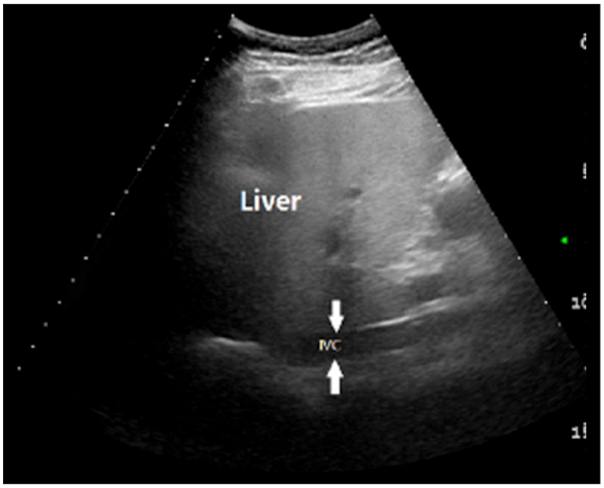

Figure 1. Measurement of IVC (arrows) on ultrasonography.

ml of saline in 4°C was injected quickly (within 5 s), measuring at least 3 times in a row, and using measurements whose variation was less than 15%.

Bedside ultrasound

A Sonosite M-TURBO ultrasound machine with a 3.5-MHz frequency probe was used to detect IVC diameter. The probe was placed in the subxiphoid location when the patient was supine. To standardize measurements, the IVC was measured 2 cm caudal to the junction point of the hepatic vein and IVC, choosing the 2-D mode every 10 s (and including 2–3 respiratory cycles). The inspiratory (IVCi) and respiratory (IVCe) diameters of the IVC were detected by measuring the vein lumen at 1 respiratory cycle, from 1 interior wall to the opposite interior wall (Figure 1). The IVCCI (IVCCI=[(IVCe–IVCi)/IVCe]×100%) was calculated as the IVC provided respiratory variation. All measurements were performed by qualified ultrasound radiologists.

Volume expansion

Before the start of treatment, HR, MAP, CVP, CI, GEDWI, ITBVI, IVCE, and IVCD were monitored as baseline parameters. During volume expansion with 500 ml of 6% hydroxyethyl starch (HES, 130/0.4) over 30 min, ventilator setting and dosages of inotropic and vasopressor drugs were held constant. After intravenous fluid was given, all measurements were repeated.

Patients were divided into 2 groups depending on change in CI after volume expansion, including the positive response group (PRG, whose CI increased 15% or more compared with baseline) and the negative response group (NRG, whose CI increased less than 15% compared with baseline). We assumed that a 15% change in CI was needed for clinical significance according to previous studies [11–13]. Therefore, patients with a CI increase induced by >15% and <15% were classified as responders and non-responders, respectively.

Statistical analysis

All data are expressed as the mean ± standard deviation and range. The paired t-test was used to compare variables that gave a normal pre-treatment and post-treatment distribution in the patient group, whereas an independent t-test was used to compare variables that gave a normal distribution between PRG and NRG. The relationship between variables was analyzed using Pearson correlation analysis. A receiver operating characteristic (ROC) curve was plotted to determine the threshold values of IVCCI, which provided the prediction of the response to volume expansion with the best sensitivity and specificity. A P-value of less than 0.05 was considered to be statistically significant.

Results

GEDVI had the strongest negative correlation with IVCCI after fluid resuscitation in both the NRG and PRG groups

HR increased after treatment in the PRG group, whereas MAP was higher in the NRG group. Other measurements (CVP, CI, GEDVI, and ITBVI) improved in both groups, while only IVCCI decreased (Table 2). Further analysis showed that IVCCI was negatively correlated with CVP, CI, and GEDVI in the 2 groups. The correlation coefficient of GEDVI was stronger than the correlation coefficient of CVP and CI in the PRG and NRG groups, respectively (Table 3). Therefore, we concluded that GEDVI had the strongest negative correlation with IVCCI in both groups.

The initial IVCCI, which was higher than 12.9%, acted as a cut-off value to discriminate a GEDCI below 600 mL/m² in the PRG group

As GEDVI had the strongest correlation with IVCCI, we further assessed the exact relationship between GEDVI and IVCCI in the PRG group. The ROC curve demonstrated that IVCCI had the best area under the curve (AUC), with 100% sensitivity and 100% specificity for a cut-off value of 0.129 to detect a GEDVI below 600 mL/m² (Figure 2, Table 4). To further evaluate the clinical usefulness of IVCCI in predicting volume expansion, we examined the change of IVCCI relationships in 7 patients in whom serial measurements of IVCCI and GEDVI were obtainable. Figure 3 shows that the initial GEDVI of all 7 patients was <600 ml/m² with a corresponding IVCCI higher than 12.9%. Importantly, 2 patients whose GEDVI increased to ≥600 ml/m² in the second measurements had concomitant decreases in IVCCI to <12.9%. These data further support the validity of IVCCI for predicting elevated GEDVI in sepsis patients.

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Table 2. Comparison between pretreatment and post-treatment group in NRG and PRG group.

Content	NRG (n=10)			PRG (n=32)		
	Pretreatment	Post-treatment	P-value	Pretreatment	Post-treatment	P-value
HR	103±16	82±18	0.042	105±12	83±12**	0.008
MAP	61±13	83±11**	0.008	69±6	86±12	0.032
CVP	5.5±2.6	8.6±1.6**	0.006	7±3	11±4**	0.008
IVCCI	21.8±7.1	14.4±4.0**	0.005	22.7±6.1	12.9±3.7**	0.004
CI	2.8±0.4	3.0±0.2	0.008	3.3±2.7	4.5±0.4**	0009
GEDVI	536±59	664±25**	0.007	638±115	905±295	0.003
ITBVI	754±66	961±83**	0.005	739±95	884±76**	0.006

P values represent the significant differences between the measurements of pretreatment and post-treatment (paired t-test).
HR – heart rate; MAP – mean arterial pressure; CVP – central venous pressure; CI – cardiac index; ITBVI – intrathoracic blood volume index; GEDVI – general heart end-diastolic volume index.

Table 3. Correlation analysis of IVCCI.

Content	NRG (n=10)		PRG (n=32)	
	r	p	r	p
CVP&IVCCI	–0.602	0.038*	–0.749	0.013*
CI&IVCCI	–0.65	0.017*	–0.789	0.007**
GEDVI&IVCCI	–0.672	0.017*	–0.889	0.000**

* P<0.05(Person correlation analysis). IVCCI has negative correlation coefficient with CVP, CI and GEDVI in both two groups. GEDVI, whose correlation coefficient was 0.889 and 0.672 respectively in each group, had the biggest correlation coefficient with IVC-CI.

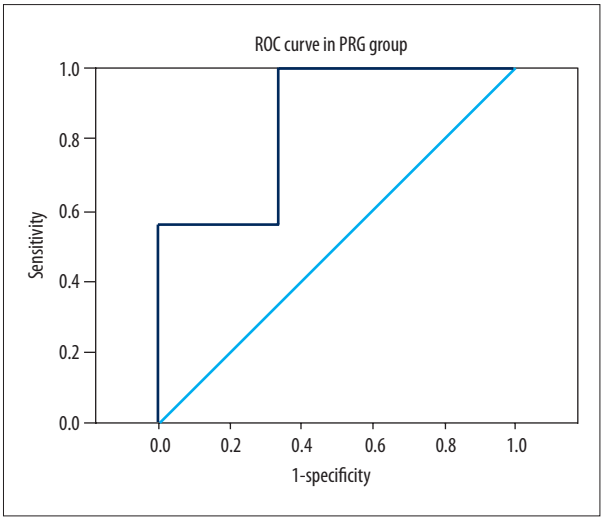

Figure 2. ROC analysis of IVCCI in predicting fluid responsiveness for a GEDWI ≤600 mL/m^2. The area under the curve was 0.917 in PRG group. Threshold values of IVCCI are given with their respective sensitivity and specificity.

Table 4. Cut-off of IVC-CI in PRG group.

PRG group		
Cut-off	Sensitivity	1-specificity
12.9*	1	1
14.6	1	0.833
15.6	1	0.677
18.6	1	0.5
22.1	1	0.333
23.05	0.75	0.167
24.4	0.5	0.25
27.05	0.5	0

* P<0.05. The ROC curve demonstrated that 0.129 of IVC-CI in PRG group had 100% sensitivity and 100% specificity for a cut-off to discrimination of GEDCI below 600 ML/m^2.

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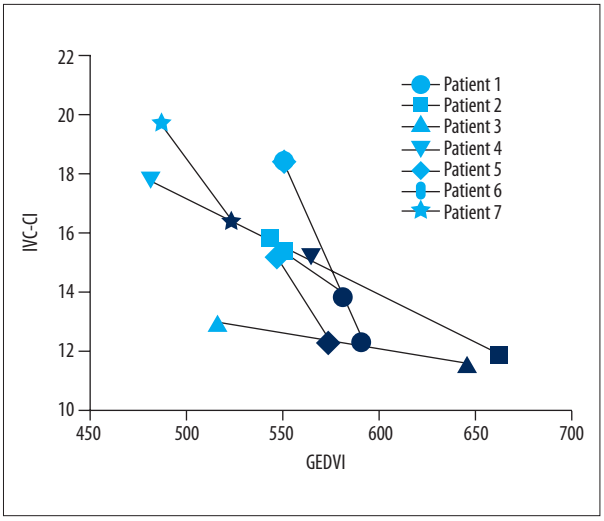

Figure 3. Serial changes in GEDVI and IVCCI. The same symbols connected by straight lines indicate identical patients. (deep blue symbols) Initial measurement; (light blue symbols) subsequent measurement.

Discussion

Cardiac preload refers to the initial length of myocardial fibers when the heart begins to shrink. Previous studies have demonstrated that GEDVI of PiCCO measurement can reflect preload. Moreover, GEDVI is not based on pressure, which may be influenced by many factors in volume expansion [14]. Therefore, PiCCO measurement is frequently used in clinical practice. However, PiCCO monitoring requires placement of a central venous catheter and a set of transducers, which is often difficult in urgent resuscitation, or impossible if the clinician is inexperienced. It also increases risk of complications [15], which makes it unsuitable for routine use during the care of septic shock patients. Therefore, bedside ultrasound is an alternative approach to estimate intravascular status and the need for fluid resuscitation.

The IVC is a highly collapsible major vein whose diameter is altered by respiration, blood volume, and right heart function [16]. Therefore, it reflects volume status and acts as a reservoir [17]. The quality of the IVC evaluation does not depend greatly on operator experience. It has already been shown that a 4-h course on ultrasound analysis of the inferior vena cava (20 clinical cases) can significantly improve clinical diagnosis of vascular overload by internal medicine residents [18]. Therefore, bedside ultrasound of the IVC is a valuable, non-invasive, and rapid hemodynamic monitoring tool for use in the intensive care unit.

Our data show that both GEDVI and IVC distensibility index, termed IVCCI, were good predictors of low volume expansion. The results of our pilot study suggest that an elevated IVCCI (greater than 12.9%) may represent a new index to detect decreased GEDVI, with a sensitivity of 100% and specificity of 100% in ill septic patients. Specifically, the increase in GEDVI during volume expansion is proportional to the measured value of IVCCI. Therefore, a qualitative assessment of IVCCI in our study should be able to detect most patients with an IVCCI of greater than 0.129 and an increase in cardiac output of more than 15% during a fluid challenge test. Even after volume expansion therapy, the GEDVI of the 4 patients with an IVCCI of greater than 0.129 was lower than 600 ml/m^2. Therefore, the IVCCI can also serve as an index to ensure lower GEDVI levels, which can be easily integrated into an overall hemodynamic assessment, as mentioned previously. Future studies with a larger sample size are warranted to test this hypothesis.

There are a number of important limitations to this study. First, IVC diameter varies widely and moves relative to the ultrasound transducer secondary to respiratory activity. Moreover, movement off the midline of the IVC results in an artificial decrease in measured diameter along the long axis [19]. Measurement may be performed in the M-mode to avoid this bias. Second, we only enrolled 42 patients in this study and the range of subjects was narrower than expected. Diseases (e.g., right heart disease, portal hypertension, and obstructive lung disease) that effect IVC diameter prevent use of this technique and limit the results of our study. Therefore, it is better to perform serial measurements to evaluate volume status more precisely, and to investigate its effect on outcomes.

Although the present study yielded some interesting results, there are also a few limitations. Actually, the same findings may be also result from hypovolemic shock. The present study is only a preliminary investigation of the role of inferior vena cava collapsibility in septic shock. In our next study, we plan explore the role of inferior vena cava collapsibility in both septic shock and hypovolemic shock.

Conclusions

An IVC distensibility index above 12.9% is a good argument in favor of volume expansion in circulatory failure during severe sepsis. Ultrasonographically-derived IVCCI is potentially useful for the management of circulation in septic shock patients.

Conflict of interests

None.

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