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Application value of bedside ultrasound for assessing volume responsiveness in patients with septic shock

Korist od primene ultrazvuka za procenu odgovora bolesnika sa septičkim šokom na nadoknadu volumena

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Abstract

Background/Aim. Septic shock (SS) is a complication that can occur as a consequence of an infection. As the effective circulating blood volume is of great importance in these cases, keeping constant track of the blood volume parameter is essential. The aim of this study was to explore the application value of bedside ultrasound for assessing volume responsiveness (VR) in patients with SS. **Methods.** A total of 102 patients with SS were selected. The volume load (VL) test was performed, and based on the results of the test, the patients were divided into two groups. The first group was the response (R) group, which had an increase in stroke volume (ΔSV) ≥ 15% after the VL test, and the second was the non-response (NR) group, with ΔSV < 15% after the VL test. There were 54 patients in the R group and 48 in the NR group. Hemodynamic parameters were compared before and after the VL test. The correlation between ΔSV and each hemodynamic index was explored by Pearson's analysis. The receiver operating characteristic (ROC) curves were plotted for some of the parameters. **Results.** Before the VL test, retrohepatic (RH) *inferior vena cava* (IVC) (RHIVC) distensibility ($\Delta_{RH}IVC_1$) index, respiratory variation in RHIVC ($\Delta_{RH}IVC_2$) index, respiratory variation in aortic (AO) blood flow peak velocity ($\Delta Vpeak_{AO}$) index, respiratory variation in brachial artery (BA) blood flow peak velocity ($\Delta Vpeak_{BA}$) index, and respiratory variation in common femoral artery (CFA) blood flow peak velocity ($\Delta Vpeak_{CFA}$) index were all higher in the R group than those in the NR group ($p < 0.05$), while heart rate (HR), mean arterial pressure (MAP), and central venous pressure (CVP) were similar in both groups ($p > 0.05$). After the VL test, the R group had significantly decreased values of HR and the $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ indices, while the MAP and CVP values ($p < 0.05$) were increased. The NR group had a significantly decreased value of CVP ($p < 0.05$), while no significant changes were noticed in the values of other indices. The indices $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ significantly correlated with ΔSV ($r = 0.589$, $r = 0.647$, $r = 0.697$, $r = 0.621$, $r = 0.766$, respectively; $p < 0.05$), but there was no correlation between CVP and ΔSV ($r = -0.345$; $p > 0.05$). The areas under the curve (AUC) of ROC graphics for $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ indices, used for the prediction of VR, were 0.839, 0.858, 0.878, 0.916, and 0.921, respectively, and were significantly larger than the AUC of ROC graphic for CVP (0.691), indicating higher sensitivity and specificity of the $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ indices compared to CVP. **Conclusion.** Bedside ultrasound monitoring of the $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ indices can assess the VR in patients with SS more precisely.

Key words:
blood volume; hemodynamic monitoring; infusions, intravenous; saline solution; shock, septic; ultrasonography.

Apstrakt

Uvod/Cilj. Septički šok (SŠ) je komplikacija koja može nastati kao posledica infekcije. S obzirom na to da je efektivni cirkulatorni volumen krvi od velike važnosti u ovim slučajevima, kontinuirano praćenje parametara volumena krvi je ključno. Cilj ovog rada je bio da se istraži značaj primene ultrazvuka za procenu odgovora na

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nadokandu volumena (*volume responsiveness* – VR) kod bolesnika sa SŠ. **Metode.** Odabrano je ukupno 102 bolesnika sa SŠ. Urađen je test volumenskog opterećenja (*volume load* – VL), i na osnovu rezultata testa, bolesnici su bili podeljeni u dve grupe. Jednu grupu činili su bolesnici koji su pokazali odgovor (*response* - R) na VL testu (grupa R); kod njih je povećanje udarnog volumena (*stroke volume*-SV) (ΔSV) bilo ≥ 15% posle VL testa. Drugu grupu (*non-response* – NR) činili su bolesnici kod kojih je ΔSV bio < 15% posle VL testa. U grupama je bilo 54 bolesnika (R) i 48 bolesnika (NR). Ispitivani hemodinamički parametri upoređivani su pre i posle VL testa. Korelacija između ΔSV i svakog pojedinačnog hemodinamičkog indeksa ispitivana je Pirsonovom analizom, a za određene parametre korišćene su ROC krive. **Rezultati.** Pre VL testa, veće vrednosti u grupi R u odnosu na grupu NR ($p < 0,05$) imali su sledeći indeksi: rastegljivost retro-hepatične ($_{RH}$) donje šuplje vene [*inferior vena cava* (IVC)] ($\Delta_{RH}IVC_1$), respiratorna varijacija $_{RH}IVC$ ($\Delta_{RH}IVC_2$), respiratorna varijacija najveće brzine protoka krvi u aorti ($\Delta Vpeak_{AO}$), respiratorna varijacija najveće brzine protoka krvi u brahijalnoj arteriji ($_{BA}$) ($\Delta Vpeak_{BA}$) i respiratorna varijacija najveće brzine protoka krvi u zajedničkoj femoralnoj arteriji [*common femoral artery* ($_{CFA}$)]($\Delta Vpeak_{CFA}$). Frekvencija srca (FS), srednji arterijski pritisak (SAP) i centralni venski pritisak (CVP) su imali slične vrednosti ($p > 0,05$) u obe grupe. Nakon VL testa, grupa R imala je značajno smanjenje vrednosti FS i indeksa $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$ i $\Delta Vpeak_{CFA}$, a povećanje vrednosti SAP i CVP ($p < 0,05$). Grupa NR imala je značajno smanjen CVP ($p < 0,05$), a nisu primećene značajne promene u vrednostima ostalih indeksa. Indeksi $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$ i $\Delta Vpeak_{CFA}$ bili su u značajnoj korelaciji sa ΔSV ($r = 0,589$, $r = 0,647$, $r = 0,697$, $r = 0,621$, $r = 0,766$, redom; $p < 0.05$), ali nije bilo korelacije između CVP i ΔSV ($r = -0,345$; $p > 0,05$). Površine ispod ROC krive [*areas under the curve* (AUC)] za indekse $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$ i $\Delta Vpeak_{CFA}$, koji su korišćeni za predviđanje VR, iznosile su 0,839, 0,858, 0,878, 0,916 i 0,921 redom, i bile su značajno veće od AUC za CVP (0,691), što je ukazivalo da su indeksi $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$ i $\Delta Vpeak_{CFA}$ imali viši nivo osetljivosti i specifičnosti u poređenju sa CVP. **Zaključak**. Ultrazvučnim praćenjem indeksa $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$ i $\Delta Vpeak_{CFA}$ može se preciznije proceniti VR kod bolesnika sa SŠ.

Ključne reči:
krv, volumen; hemodinamika, monitoring; infuzije, intravenske; rastvor, fiziološki; šok, septički; ultrasonografija.

Introduction

Septic shock (SS) is primarily caused by hemodynamic instability due to various pathogen infections, and it is characterized by high cardiac output (CO), low peripheral vascular resistance, and the resulting sepsis-induced tissue hypoperfusion. SS has a high mortality rate and many complications, which are more common in the Intensive Care Unit (ICU) [1–3]. At present, fluid resuscitation (FR) is an important strategy for the clinical treatment of SS, which can supplement the effective circulating blood volume, improve tissue perfusion, and correct cellular hypoxia, thereby lowering the mortality rate [4, 5]. According to the Frank-Starling Law of the heart, the cardiac reserve is sufficient among patients in the ascending branch of the curve, and the increase in cardiac preload within a certain range can increase CO and fully achieve FR. However, when the left or right ventricle is at the plateau of the Frank-Starling curve, excessive FR will worsen the cardiac volume load (VL) in patients, raise the risk of pulmonary edema and decreased oxygenation, and aggravate shock [6]. After early rapid FR, however, it is difficult to assess the patient's blood volume status. Excessive FR will induce complications such as heart failure and pulmonary edema, while insufficient FR will increase the risk of organ dysfunction in patients [7, 8]. Therefore, it is essential to accurately assess the volume responsiveness (VR) in patients with SS for FR therapy. Bedside ultrasound can dynamically predict and evaluate the responsiveness of the circulatory system to the VL in convenient, non-invasive, and real-time manners. Full attention has been given to it in hemodynamic assessment in patients with SS. In this study, the hemodynamic indices of VR in patients with SS were observed by bedside ultrasound, and the value of ultrasound hemodynamic indices in assessing the VR was explored to provide a theoretical basis for fluid therapy in patients with SS.

Methods

A total of 102 patients with SS who received mechanical ventilation (mode: AC/PC; PS: 15 cmH_2O; PEEP: 4 cmH_2O; FIO_2: 45%) in Jinshan Hospital, China, from April 2018 to February 2021 were selected, including 55 males and 47 females aged 23–75 years. The patients had an average age of 56.4 ± 12.4 years. Inclusion criteria were as follows: 1) patients meeting the diagnostic criteria for SS in the "International Guidelines for Management of Sepsis and Septic Shock: 2016" [9]; 2) patients with any of the following clinical manifestations of tissue hypoperfusion – a) systolic blood pressure (SBP) ≤ 90 mmHg (decline in SBP > 50 mmHg in hypertensive patients); b) heart rate (HR) >100 bpm; c) urine volume < 0.5 mL/kg for two consecutive hours; d) piebald skin; 3) patients with sinus HR.

Exclusion criteria were as follows: 1) patients with intra-abdominal hypertension; 2) patients with congenital heart disease, severe cardiac insufficiency, severe arrhythmia or pulmonary arterial hypertension; 3) patients with severe obesity, i.e., body mass index (BMI) > 40 kg/m^2; 4) patients with complications such as cerebrovascular accident, neurogenic shock, coronary heart disease or intra-aortic balloon counterpulsation; 5) pregnant women; 6) those with contraindications for fluid infusion (left ventricular ejection fraction – LVEF ≤ 40%, lower limb vein thrombosis, aortic valve or pulmonary valve disease, mitral valve stenosis or insufficiency > degree 2, or volume overload).

General clinical data of patients (gender, age, BMI, and infection site), acute physiology and chronic health evaluation II (APACHE II) score, and sequential organ failure assessment (SOFA) score were recorded within 24 hrs after entering the ICU.

The patients were given effective analgesia and sedation in a supine position, and 200 mL of normal saline was quickly infused *via* the central vein within ten minutes. Blood volume supplementation was terminated when the patient's central venous pressure (CVP) reached the value of more than 5.0 cm H_2O (1 cm H_2O = 0.098 kPa), and the increase in stroke volume (ΔSV) was less than 10% of the basal level, or when obvious pulmonary edema occurred. Before and after the VL test, hemodynamic monitoring was performed. Transthoracic echocardiography was conducted using a Zonare color Doppler ultrasound diagnostic apparatus (P4-1C probe, frequency: 3.5 MHz). Left ventricular outflow tract dimension was measured in the left ventricle long-axis view, and one complete respiration cycle was monitored in the apical five-chamber view in order to obtain the left ventricular outflow tract velocity-time integral (VTI) and the maximum ($Vpeak_{max}$) and minimum value ($Vpeak_{min}$) of the aortic ($_{AO}$) blood flow peak velocity with respiratory motion. The retro-hepatic ($_{RH}$) *inferior vena cava* (IVC) ($_{RH}$IVC) was explored by the probe longitudinally below the right rib; the minimum end-inspiratory dimension (D_{min}) and the maximum end-expiratory dimension (D_{max}) of IVC were monitored in the subxiphoid IVC long-axis view during one complete respiration cycle. Then the brachial artery ($_{BA}$) blood flow velocity was measured at the cubital *fossa* using the L10-5 probe (frequency 8 MHz), and the $Vpeak_{max}$ and $Vpeak_{min}$ of the ($_{BA}$) blood flow peak velocity with respiratory motion were monitored during one complete respiration cycle. The same parameters were measured for the common femoral artery ($_{CFA}$).

The above indices were measured three times, and the average value was taken. Moreover, CO, ΔSV, distensibility of $_{RH}$IVC ($\Delta\ _{RH}IVC_1$) index, respiratory variation in $_{RH}$IVC ($\Delta_{RH}IVC_2$) index, respiratory variation in ($_{AO}$) blood flow peak velocity ($\Delta Vpeak_{AO}$) index, respiratory variation in ($_{BA}$) blood flow peak velocity ($\Delta Vpeak_{BA}$) index, and respiratory variation in ($_{CFA}$) blood flow peak velocity ($\Delta Vpeak_{CFA}$) index were calculated using the following formulas:

$$SV = (D/2)^2 \times \pi \times VTI$$

$$\Delta SV = (SV_{load\ value} - SV_{basal\ value}) / SV_{basal\ value}$$

$$\Delta_{RH}IVC_1 = (D_{max} - D_{min}) / D_{min} \times 100\%$$

$$\Delta_{RH}IVC_2 = 2 \times (D_{max} - D_{min}) / (D_{max} + D_{min}) \times 100\%$$

$$\Delta Vpeak_{AO} = 2 \times (Vpeak_{max} - Vpeak_{min}) / (Vpeak_{max} + Vpeak_{min}) \times 100\%$$

$$\Delta Vpeak_{BA} = 2 \times (Vpeak_{max} - Vpeak_{min}) / (Vpeak_{max} + Vpeak_{min}) \times 100\%$$

$$\Delta Vpeak_{CFA} = 2 \times (Vpeak_{max} - Vpeak_{min}) / (Vpeak_{max} + Vpeak_{min}) \times 100\%$$

where the $Vpeak_{max}$ is the maximum value of blood flow peak velocity during one respiration cycle for each of the mentioned blood vessels, and $Vpeak_{min}$ is the minimum value of blood flow peak velocity during one respiration cycle for each of the mentioned blood vessels.

Based on ΔSV after fluid infusion, the patients were divided into the positive volume response (R) group ($\Delta SV \geq 15\%$) and the non-response (NR) group ($\Delta SV < 15\%$).

SPSS 22.0 software was used for statistical analysis. Normally distributed measurement data were expressed as mean ± standard deviation and compared between two groups by independent-samples *t*-test. Numerical data were expressed as a percent and compared between two groups by χ^2 test. The correlation between ΔSV and each hemodynamic index was explored by Pearson's analysis. The receiver operating characteristic (ROC) curve was plotted; the value of the hemodynamic index for assessing the VR in patients with SS was analyzed. The value of $p < 0.05$ was considered statistically significant.

Results

Among the 102 patients with SS, there were 40 cases of pulmonary infection, 10 cases of intracranial infection, 18 cases of abdominal infection, 16 cases of urinary system infection, 14 cases of blood-borne infection, and four cases of other types of infection. Fifty-four (52.9%) patients had a positive volume response. At the baseline, the patient's gender, age, BMI, tidal volume, respiratory rate, LVEF, SBP, lactic acid level, APACHE II score, SOFA score, shock index, and infection site had no significant differences between positive volume response (R) patients, and negative volume response (NR) patients ($p > 0.05$), indicating that the baseline data were comparable (Table 1).

There were no significant differences in HR, CO, mean arterial pressure (MAP), and CVP between the two groups before the VL test ($p > 0.05$). After the VL test, HR declined, while CO, MAP, and CVP rose in R patients ($p < 0.05$). After the VL test, CO and CVP rose in NR patients ($p < 0.05$), while HR and MAP had no significant changes. After the VL test, the R group had lower HR and higher CO and MAP than the NR group ($p < 0.05$) (Table 2).

Before the VL test, the $\Delta\ _{RH}IVC_1$, $\Delta\ _{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ indices were all higher in the R group compared to the NR group ($p < 0.05$). After the VL test, the $\Delta_{RH}IVC_1$, $\Delta\ _{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ indices declined to different levels in the two groups. There were significant differences in the values of the parameters before and after the VL test in R patients ($p < 0.05$), while there were no significant changes before and after the VL test in NR patients ($p > 0.05$) (Table 3).

CO and the $\Delta\ _{RH}IVC_1$, $\Delta\ _{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ indices were significantly correlated with ΔSV before the VL test ($r = -0.672$, $r = 0.589$, $r = 0.647$, $r = 0.697$, $r = 0.621$, $r = 0.766$, respectively; $p < 0.05$), but there was no correlation between CVP and ΔSV ($r = -0.345$; $p > 0.05$). The results showed that ultrasonically measured hemodynamic indices before the VL test could be used to assess VR in patients with SS (Table 4).

The area under the curve (AUC) of ROC graphics for CO and the $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and

Table 1

Baseline clinical data of patients

Parameter	Response group (n = 54)	Non-response group (n = 48)	t/χ^2	*p*-value
Age (years)	54.9 ± 10.3	57.8 ± 11.9	0.724	0.468
BMI (kg/m^2)	23.3 ± 3.7	23.7 ± 3.6	0.468	0.635
TV (mL)	556.9 ± 87.9	528.9 ± 72.8	1.162	0.258
RR (time/min)	19.1 ± 3.4	18.9 ± 3.2	0.697	0.502
LVEF (%)	58.7 ± 10.3	59.2 ± 11.0	0.236	0.805
SBP (mmHg)	115.3 ± 21.1	113.0 ± 22.3	0.413	0.681
Lactic acid (mmol/L)	2.5 ± 0.6	2.7 ± 0.6	1.470	0.146
APACHE II score	27.6 ± 9.4	26.3 ± 10.2	0.320	0.742
SOFA score	10.4 ± 3.1	10.0 ± 1.1	0.285	0.821
Shock index	1.4 ± 0.4	1.3 ± 0.5	1.086	0.267
Infection site				
pulmonary infection	21 (38.9)	19 (39.6)	0.299	0.765
intracranial infection	4 (7.4)	6 (12.5)	2.668	0.258
abdominal infection	10 (18.5)	8 (16.7)	1.963	0.167
urinary system infection	9 (16.7)	7 (14.6)	0.049	0.976
blood-borne infection	7 (12.9)	7 (14.7)	0.946	0.514
other	3 (5.6)	1 (2.1)	0.422	0.685

BMI − body mass index; TV − tidal volume; RR − respiratory rate; LVEF − left ventricular ejection fraction; SBP − systolic blood pressure; APACHE II − acute physiology and chronic health evaluation II; SOFA − score and sequential organ failure assessment.
Results are shown as mean ± standard deviation except infection sites which are shown as numbers (percentages).

Table 2

General hemodynamic indices before and after the volume load test

Parameter	Before	After	*t*	*p*-value
Response group (n = 54)				
HR (beats/min)	118.7 ± 9.2	113.0 ± 8.9	4.534	**0.001**
MAP (mmHg)	67.2 ± 7.8	73.0 ± 7.2	-3.845	**0.003**
CVP (cmH_2O)	6.9 ± 1.4	9.3 ± 1.5	-7.034	**< 0.001**
CO (L/min)	6.2 ± 0.7	8.3 ± 1.0	12.465	**< 0.001**
Non-response group (n = 48)				
HR (beats/min)	118.7 ± 9.2	117.0 ± 8.5*	-1.021	0.284
MAP (mmHg)	70.4 ±7.4	71.1 ± 7.8*	-1.883	0.125
CVP (cm H_2O)	7.1 ± 1.4	9.2 ± 1.8	-5.969	**0.001**
CO (L/min)	6.2 ± 0.6	6.2 ± 0.7*	0.219	0.827

HR − heart rate; MAP − mean arterial pressure; CVP − central venous pressure; CO − cardiac output.
Bolded values are statistically significant; $^*p < 0.05$ vs. response group.
Results are shown as mean ± standard deviation.

Table 3

Ultrasound hemodynamic indices before and after the volume load (VL) test

Parameter	$\Delta_{RH}IVC_1$	$\Delta_{RH}IVC_2$	$\Delta Vpeak_{AO}$	$\Delta Vpeak_{BA}$	$\Delta Vpeak_{CFA}$
Response group (n = 54)					
before the VL test	19.1 ± 3.4	17.4 ± 3.4	14.9 ± 1.4	16.2 ± 1.4	17.0 ± 2.4
after the VL test	16.0 ± 4.0	15.0 ± 3.1	12.1 ± 1.2	13.2 ± 1.3	16.1 ± 2.2
t	5.109	7.568	10.645	8.174	4.730
p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Non-response group (n = 48)					
before the VL test	14.4 ± 2.6*	13.6 ± 2.2*	12.6 ± 1.5*	13.4 ± 1.9*	11.9 ± 2.6*
after the VL test	14.2 ± 2.6	13.2 ± 1.8	12.5 ± 1.3	13.2 ± 1.9	11.8 ± 2.8
t	0.998	1.789	1.146	1.523	1.702
p-value	0.328	0.089	0.253	0.145	0.106

$\Delta_{RH}IVC_1$ − index of distensibility of retro-hepatic ($_{RH}$) *inferior vena cava* (IVC)($_{RH}$IVC); $\Delta_{RH}IVC_2$ − index of respiratory variation in $_{RH}$IVC; $\Delta Vpeak_{AO}$ − index of respiratory variation in aortic ($_{AO}$) blood flow peak velocity; $\Delta Vpeak_{BA}$− index of respiratory variation in brachial artery ($_{BA}$) blood flow peak velocity; $\Delta Vpeak_{CFA}$ − index of respiratory variation in common femoral artery blood flow peak velocity. Results are shown as mean ± standard deviation. Bolded values are statistically significant; $^*p < 0.05$ vs. response group.

Table 4

Correlation between the increase in stroke volume and each hemodynamic index before the volume load test

ΔSV	CVP	$\Delta_{RH}IVC_1$	$\Delta_{RH}IVC_2$	$\Delta Vpeak_{AO}$	$\Delta Vpeak_{BA}$	$\Delta Vpeak_{CFA}$
r	-0.345	0.589	0.647	0.697	0.621	0.766
p-value	0.135	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**

ΔSV − increase in stroke volume; CVP − central venous pressure. For the abbreviations of other indices see Table 3. Bolded values are statistically significant.

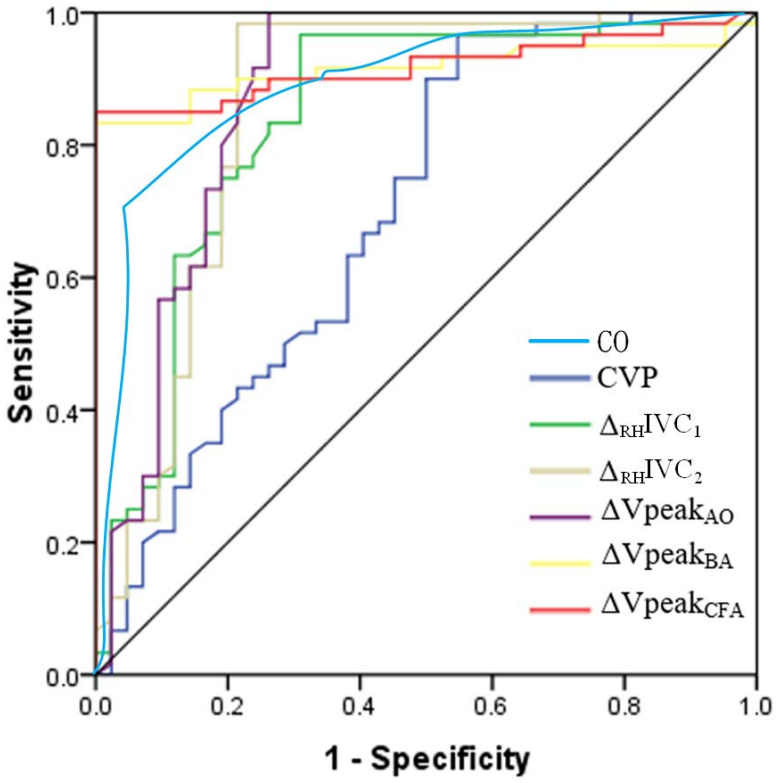

Fig. 1 – Receiver operating characteristic curves of hemodynamic indices for assessing VR in patients with septic shock. CO – cardiac output. For the abbreviations see Table 3.

Table 5

Receiver operating characteristic curve analysis results of each hemodynamic index for assessing volume responsiveness before the volume load test

Index	CVP	$\Delta_{RH}IVC_1$	$\Delta_{RH}IVC_2$	$\Delta Vpeak_{AO}$	$\Delta Vpeak_{BA}$	$\Delta Vpeak_{CFA}$
AUC	0.691	0.839	0.858	0.878	0.916	0.921
95% CI	0.431~0.792	0.705~0.973	0.796~0.923	0.820~0.952	0.785~0.997	0.866~0.978
p-value	0.229	**0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Optimal cutoff value (%)	6.2	17.5	16.5	13.5	14.7	15.5
Sensitivity (%)	55.2	65.4	65.4	84.4	70.4	75.2
Specificity (%)	74.8	84.9	84.9	72.7	81.8	85.3
Positive predictive value (%)	76.8	77.8	77.8	93.2	88.8	93.3
Negative predictive value (%)	71.7	72.7	72.7	79.2	68.9	76.0

AUC − area under the curve; CI − confidence interval. Bolded values are statistically significant. For the abbreviations see Table 3.

$\Delta Vpeak_{CFA}$ indices before the VL test, intended for prediction of the VR, all exceeded the value of 0.8, which was significantly higher than the AUC of ROC graphic for CVP, indicating higher sensitivity and specificity of the mentioned indices (Figure 1; Table 5).

Discussion

At present, FR is one of the most effective methods for managing shock in the clinic, but it is also necessary to determine the VR in patients. There is a study showing that on-

ly 50% of patients with hemodynamic instability had VR. Among them, VR was found in only 43.5% of septic patients. Therefore, assessing the volume status and responsiveness of patients with SS is the key to determining whether further FR can be performed [6]. Bedside, ultrasound can reflect the volume status of patients with SS, which has recently been paid extensive attention to in the field of critical care medicine in China and foreign countries [10]. Currently, VR is predicted mainly through the assessment of SV by the VL test and mini rehydration test combined with ultrasound. These methods are not affected by the patient's ventilation mode and cardiac rhythm, with high sensitivity and specificity, which can assess the VR well.

The blood volume status of patients was mainly determined by HR, blood pressure, and urine volume previously, but the effect was unsatisfactory. CVP is close to the right atrial pressure and can be monitored easily in a highly operable manner, which can be used to determine the VR indirectly. However, CVP may be affected by the positive end-expiratory pressure during mechanical ventilation, leading to distorted results, so there are certain limitations [11, 12]. In this study, CVP had a significant difference before and after the VL test in R and NR patients, indicating that CVP has a certain value in assessing the VR in patients with SS.

It has been found that there is a high consistency between continuous monitoring of CO and measurement of SV by transthoracic echocardiography in predicting fluid responsiveness [13]. The IVC is a capacity vessel characterized by a large inner diameter and good compliance, and its lumen diameter changes with respiration. The blood volume in patients with SS declines considerably, which leads to a decrease in IVC lumen diameter and an increase in variation during respiration. The thoracic pressure of critically ill patients who cannot breathe spontaneously and receive mechanical ventilation increases during inhalation, and the IVC blood backflow to the right atrium decreases, expanding the IVC inner diameter; in contrast, the IVC inner diameter decreases during exhalation [14]. Therefore, VR in patients is often assessed by ultrasonic measurement of $\Delta_{RH}IVC_1$ and $\Delta_{RH}IVC_2$ in clinical conditions. It has been confirmed that the respiratory variation in IVC diameter is an accurate predictor for the VR under the ventilation mode of tidal volume ≥ 8 mL/kg and positive end-expiratory pressure ≤ 5 cm H_2O (1 cm H_2O = 0.098 kPa), with sensitivity and specificity of 80% and 94%, respectively [15]. In this study, the results revealed that both $\Delta_{RH}IVC_1$ and $\Delta_{RH}IVC_2$ in R patients were significantly higher than those in NR patients before the VL test. After the VL test, $\Delta_{RH}IVC_1$ and $\Delta_{RH}IVC_2$ significantly declined in the R group, while they had no significant changes in the NR group. $\Delta_{RH}IVC_1$ and $\Delta_{RH}IVC_2$ were significantly correlated with ΔSV before the VL test. The results of ROC curve analysis showed that $\Delta_{RH}IVC_1$ and $\Delta_{RH}IVC_2$ had higher sensitivity and specificity in predicting the VR in patients, which is consistent with the findings of Huan et al. [16]. To sum up, $\Delta_{RH}IVC_1$ and $\Delta_{RH}IVC_2$ can be used to guide the FR therapy in the clinical treatment. $\Delta Vpeak_{AO}$ can reflect the degree of dependence of the patient's circulatory system on cardiac preload, which has the closest correlation with left ventricular SV, but its transesophageal monitoring has a certain technical difficulty [17]. The ultrasonic image of the $_{BA}$ with a large inner diameter and superficial location is clear, and its monitoring is highly reliable, so the sensitivity and specificity of $\Delta Vpeak_{BA}$ in predicting VR are higher than 90% [18]. $\Delta Vpeak_{CFA}$ is prone to disturbance by intra-abdominal arterial pressure, but its accuracy in predicting the VR of mechanically ventilated patients is higher if its value changes ≥ 12% during deep inspiration [19]. In this study, the results showed that $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ in the R group were significantly higher than those in the NR group before the VL test. After the VL test, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ declined in the R group, while they had no significant changes in the NR group. According to correlation analysis, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ were significantly correlated with ΔSV before the VL test, suggesting that cardiac indices and peripheral artery indices can better predict the VR in patients and provide references for clinical volume therapy. Besides, the results of ROC curve analysis showed that both sensitivity and specificity of $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ were higher in predicting the VR under a cutoff value of 13.5, 14.7, and 15.5, respectively, which is consistent with the research results of Seif et al. [20].

Conclusion

In conclusion, bedside ultrasound monitoring of $\Delta_{RH}IVC_1$, $\Delta_{RH}IVC_2$, $\Delta Vpeak_{AO}$, $\Delta Vpeak_{BA}$, and $\Delta Vpeak_{CFA}$ can better assess the VR in patients with SS and provide a basis for clinical FR therapy. Regardless, this study is limited since it is a single-center study with a small sample size, so the results may be biased. Further multicenter studies with larger sample sizes are ongoing in our group.

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Conflict of interest

The authors declare no conflict of interest.

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