

Effect of VTI_{LVOT} variation rate on the assessment of fluid responsiveness in septic shock patients

Jinzhong Wang, MD^a, Dexing Zhou, MD^b, Yi Gao, MD^c, Zhongyong Wu, MD^a, Xiaozhi Wang, MD^{a,*}, Chuanzhu Lv, MD^{d,*}

Abstract

This study aimed to assess the predictive value of velocity time integral (VTI) of the left ventricular outflow tract (LVOT) on volume expansion test (VET) as an indicator of volume responsiveness in septic shock patients. Septic shock patients undergoing mechanical ventilation were recruited. The hemodynamic parameters before and after VE were monitored by pulse indicated continuous cardiac output (PiCCO) and echocardiography. Heart rate, cardiac index (CI), mean arterial pressure (MAP), central venous pressure, stroke volume variation (SVV), CI and variation of pulse pressure (PPV), and the changes in cardiac parameters (Dheart rate, Dmean arterial pressure, Dcentral venous pressure, DSVV, DCI, and DPPV) were determined. The relationships of hemodynamic parameters and their changes with DVTI were further evaluated with Pearson relation analysis. The value of these parameters in fluid responsiveness prediction was evaluated by using the receiver operating characteristic (ROC) curve analysis. Results showed that 44 VETs were performed in 44 septic shock patients with responsiveness in 24 patients and non-responsiveness in 20. The CI increased by $\geq 15\%$ in responsive patients, but by $< 15\%$ in non-responsive patients after VET. There were significant differences in the SVV and PPV after VET between responsive and non-responsive groups. DSVV, DPPV, and DCI were positively related to DVTI. The area under ROC curve (AUC) for SVV in fluid responsiveness prediction was 0.80, and the sensitivity and specificity of SVV were 66.5% and 95%, respectively, when the cut-off value was 24.8%. The AUC for PPV in fluid responsiveness prediction was 0.843, and the sensitivity and specificity of PPV were 83.3% and 75%, respectively, when the cut-off value was 25.8%. The AUC for DVTILVOT in fluid responsiveness prediction was 0.956, and the sensitivity and specificity were 87.5% and 95%, respectively, when the cut-off value was 15.9%. In conclusion, DVTILVOT is effective to predict fluid responsiveness after VET in mechanical ventilation patients with septic shock. It may serve as a new, noninvasive and functional hemodynamic parameter with the same accuracy to SVV.

Abbreviations: AUC = area under the curve, BP = blood pressure, CI = cardiac index, CVP = central venous pressure, HR = heart rate, LVOT = left ventricular outflow tract, MAP = mean arterial pressure, PiCCO = pulse index continuous cardiac output, PPV = pulse-pressure variability, SVV = stroke volume variation, VTI = velocity time integral.

Keywords: fluid responsiveness, septic shock, transthoracic echocardiography, velocity time integral of the left ventricular outflow tract

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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1. Introduction

Fluid resuscitation is an indispensable treatment for patients with septic shock because it can ensure adequate organ perfusion, improving the patient's prognosis. However, volume overload may increase the complications and mortality.^[1–3] Therefore, the volume status and the “fluid responsiveness” of patients should be correctly assessed before rehydration to avoid volume overload.^[4] The current gold standard for the assessment of fluid responsiveness is the change in the stroke volume after fluid boluses or simulated fluid boluses,^[5] and the fluid responsiveness is often defined as an increase of 10% to 15% or more in the cardiac output or stroke volume, or fluid non-responsiveness is defined.^[6]

The traditional static indicators including central venous pressure (CVP) have been shown to be incapable of assessing fluid responsiveness.^[7] The pulse index continuous cardiac output (PiCCO) has been used as the “gold standard” for the assessment of fluid responsiveness,^[8] and it can also be employed to monitor the cardiopulmonary interaction based dynamic indicators such as pulse-pressure variability (PPV) and stroke volume variation (SVV), with high predictive value in the fluid responsiveness assessment.^[9] However, it is an invasive procedure, has the risk for catheter infection, and is expensive, which significantly limit its wide application in clinical practice. In recent years, echocardiography plays an important role in the prediction of

fluid responsiveness with the wide application of bedside color doppler ultrasonography.^[10] Currently, echocardiography is mainly done to measure the peripheral blood related indicators (such as inferior vena cava diameter variability, carotid flow variability and radial artery peak flow rate) with good predictive value. There is evidence showing that, in patients with mechanical ventilation who receive complete sedation, the rate of superior and inferior vena cava collapse can be used to predict the fluid responsiveness,^[11,12] but it is highly susceptible to the change in pressure because it is a peripheral large venous system. Via et al found that the ventilator parameters (tidal volume less than 8 mL/kg), the spontaneous breathing, right cardiac dysfunction, abdominally high blood pressure and other factors significantly affected the predictive ability of superior and inferior vena cava because it is difficult to rule out above factors in critically ill patients,^[13] which also limit its wide application. Hilbert et al^[14] investigated the role of carotid artery diameter dilatation index in the prediction of fluid responsiveness, and their results showed it was closely related to the PPV ($r=0.56$), suggesting the predictive value of carotid artery diameter dilatation index. However, various factors such as abdominal high pressure, right heart dysfunction and arteriosclerosis can affect the sensitivity and specificity of the above parameters, and thus they often fail to reflect the actual volume status of patients. Nevertheless, the cross-sectional area of the aortic annulus remains constant during the respiratory cycle. The left ventricular outflow tract (LVOT) is the origin of cardiac output. On the transthoracic echocardiography (TTE), sampling can be done at the level approximately 2 mm below the aortic annulus from the apical 5-chamber view, and then the blood flow velocity waveform can be obtained in each cardiac cycle. Subsequently, the velocity time integral (VTI) of the LVOT (VTI_{LVOT}) was determined. The variation of VTI_{LVOT} (ΔVTI) can be calculated as follows: $\Delta VTI (\%) = (VTI_{max} - VTI_{min}) / [(VTI_{max} + VTI_{min}) / 2] \times 100\%$, where VTI_{max} and VTI_{min} represent the maximum and minimum VTI in 10 cardiac cycles. ΔVTI can reflect the change in left ventricular stroke volume, is less affected by the peripheral vascular compliance and abdominal pressure and thus can be employed to predict the fluid responsiveness.

In the present study, the change in VTI, PiCCO and factors related to fluid responsiveness were detected in septic shock patients in the intensive care unit (ICU) and to assess the predictive value of VTI_{LVOT} in the fluid responsiveness. Our findings may provide a non-invasive, repeatedly used and low-cost tool to aid the fluid resuscitation in patients with septic shock.

2. Materials and methods

2.1. Subjects

This was a prospective cohort study, and patients who received PiCCO monitoring in the Intensive Care Unit of the Second Affiliated Hospital of Hainan Medical College were recruited between January 2018 and November 2018 (Fig. 1). The measurements in this study were routine procedures and therefore not harmful, and did not increase the medical cost in these patients. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Hainan Medical College and informed consent was obtained from the family members of these patients before study.

Inclusion criteria: septic shock was diagnosed according to the diagnostic criteria in the Guideline for the Diagnosis and Treatment of Septic Shock (2016) developed by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine: sepsis is present; sepsis related persistent hypotension remains after adequate fluid resuscitation (30 mL/kg); medication is needed to maintain the mean arterial pressure (MAP) at ≥ 65 mm Hg; the serum lactic acid is >2 mmol/L.

Exclusion criteria:

- 1) brain death;
- 2) acute myocardial infarction requiring intra-aortic balloon pump (IABP) support;
- 3) receiving extracorporeal membrane oxygenation (ECMO);
- 4) persistent arrhythmia;
- 5) chronic renal failure with creatinine clearance rate (Ccr) <30 , or ongoing renal replacement therapy;
- 6) valvular heart disease with reflux;
- 7) <18 years old;
- 8) high abdominal pressure.

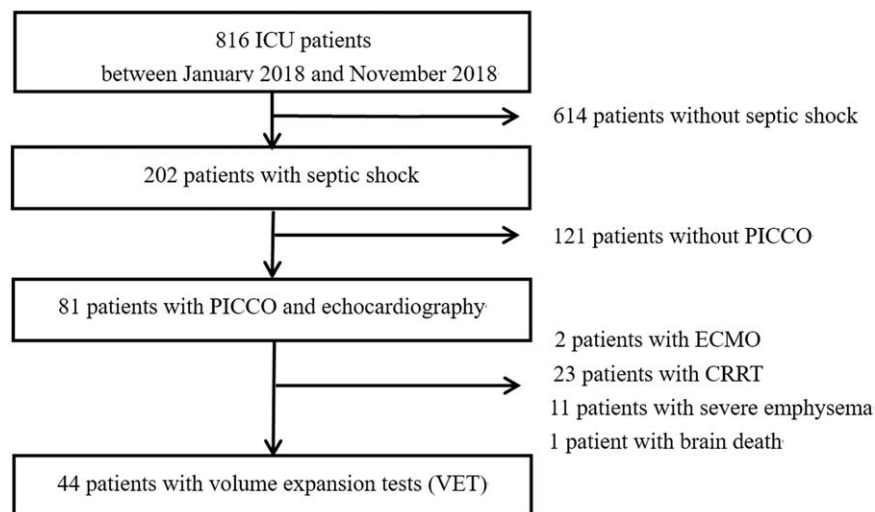


Figure 1. Flow diagram of patient inclusion.

Routine treatments: after admission, the vital signs were continuously monitored (BeneVision type, MINDRAY). According to the recommendations in the 2016 Surviving Sepsis Campaign guideline, all the patients received anti-infective treatment within 1 hour, and fluid resuscitation was performed at 30 mL/kg within 3 hour. Thereafter, the blood pressure (BP) was assessed, and standardized treatments were administered (blood glucose control, drainage of infective lesions, adequate sedation and analgesia, mechanical ventilation). Mechanical ventilation was administered at 8 to 10 mL/kg. Patients underwent volume expansion test (VET) according to the standard protocol. The rapid rehydration test was performed with intravenous infusion of 0.9% sodium chloride (500 mL) within 15 minute.

General characteristics: the demographics were recorded before VET, including gender, age and body mass index (BMI). The BP, heart rate (HR), SOFA score, acute physiology and chronic health evaluation score, dosages of vasoactive drugs and other indicators were also recorded.

Monitoring of PiCCO: the subclavian central venous PiCCO catheter (PulsioCath PV2015 L20; Pulsion Medical Systems; Munich, Germany) was placed, and data were collected with the thermodilution method. The cardiac index (CI), SVV, PPV, MAP and other data were recorded. The PiCCO data were collected within 10 minute after fluid boluses, and the Δ CVP, Δ SVV, Δ PPV, and Δ CI were calculated. The cardiac output index (Δ CI%) $\geq 15\%$ after fluid boluses was defined as fluid responsiveness (R), or fluid non-responsiveness (NR) was defined.^[6]

$$\Delta CI (\%) = [(CI_{[after]} - CI_{[before]}) / CI_{[before]}] \times 100\%;$$

$$\Delta CVP = CVP_{[after]} - CVP_{[before]}$$

$$\Delta SVV = [|SVV_{[before]} - SVV_{[after]}| / SVV_{[before]}] \times 100\%$$

$$\Delta PPV = [|PPV_{[before]} - PPV_{[after]}| / PPV_{[before]}] \times 100\%$$

Color Doppler ultrasonography: before the rapid fluid resuscitation, the patient was placed in a supine position, color doppler ultrasonography was performed using the MINDRAY M9CVcolor ultrasound diagnostic apparatus (SP5-1S cardiac probe, frequency of 3.5 MHz, pulsed doppler mode) from an apical 4 chamber view to view the LVOT as well as the blood flow velocity waveform at the level about 2 mm below the central aortic annulus. The blood flow velocity waveforms were collected within 10 cardiac cycle (Fig. 2), the VTI was measured by tracing the spectral doppler envelope, and the maximum and minimum were recorded to calculate Δ VTI. Color ultrasonography was performed by the same experienced physician. The Δ VTI was calculated as follow: $\Delta VTI (\%) = (VTI_{max} - VTI_{min}) / [(VTI_{max} + VTI_{min}) / 2] \times 100\%$.

2.2. Statistical analysis

Statistical analysis was performed with Statistical Product and Service Solutions (SPSS) version 23.0. Kolmogorov-Smirnov test was used to analyze the normal distribution of quantitative data. Quantitative data with normal distribution are presented $x \pm$ standard deviation (SD) and were compared with paired *t* test or independent sample *t* test. Data with abnormal distribution were compared with Wilcoxon test. Qualitative data were compared with χ^2 test. The correlation analysis was performed with Pearson correlation analysis. The receiver operating characteristic (ROC) curves of Δ CVP, Δ SVV, Δ PPV, and Δ VTI were plotted and the area under the curve (AUC) and 95% confidence interval (95% CI) were determined. The larger the AUC, the stronger the predictive value was. The AUC < 0.5 was suggestive of no predictive value. A value of $P < .05$ was considered statistically significant.

3. Results

3.1. General characteristics

Initially, 816 patients were admitted to the ICU between January 2018 and November 2018. Of these patients, 202 were diagnosed with septic shock, and 614 patients without septic shock were

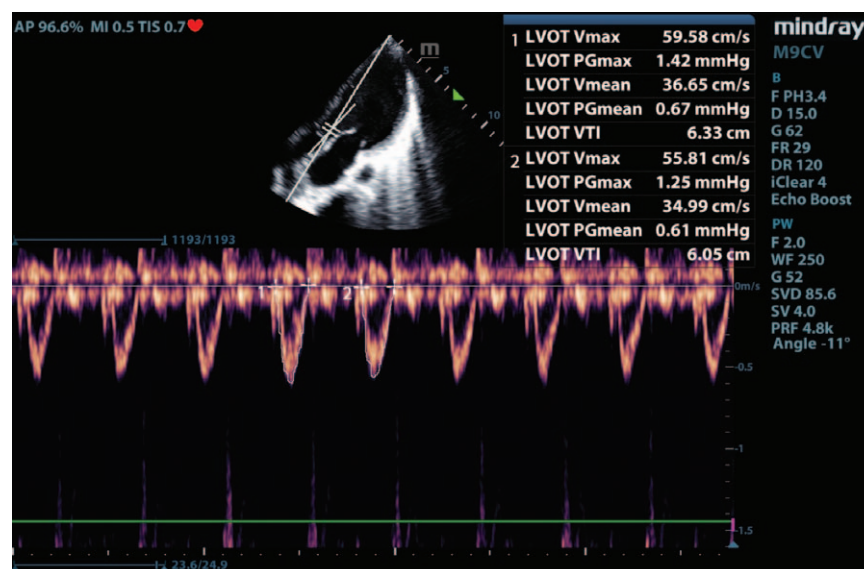


Figure 2. Left ventricular outflow tract time rate integral variability on chest doppler ultrasonography.

Table 1
Clinical characteristics of 44 patients.

Characteristics	R group (n=24)	NR group (n=20)	P
Age (yr)	58.34 ± 14.57	59.24 ± 15.72	.320
Gender (n)			
Male	14	9	
Female	10	11	
APACHE II score	22.46 ± 3.23	23.57 ± 2.46	.624
SOFA score	8.62 ± 2.47	7.62 ± 1.96	.681
Norepinephrine $\mu\text{g}/(\text{kg}\cdot\text{min})$	0.59 ± 0.57	0.62 ± 0.41	.572
HR (beats/min)	120.87 ± 8.71	121.91 ± 9.6	.857
MAP (mm Hg)	62.33 ± 4.68	61.85 ± 6.82	.783
CVP (cmH ₂ O)	8.04 ± 4.43	9.50 ± 4.25	.274
BMI (kg/m ²)	22.57 ± 0.86	21.48 ± 1.08	.328

BMI=body mass index, CVP=central venous pressure, HR=heart rate, MAP=mean arterial pressure.

excluded. In 202 patients, 121 had no PICCO and then excluded. In the remaining 81 patients with PICCO and echocardiography, 2 with ECMO, 23 with CRRT, 11 with severe emphysema and 1 with brain death were excluded. The remaining 44 patients receiving VET were included for final analysis (Fig. 1). These patients received a total of 44 fluid boluses. According to the fluid responsiveness, patients were grouped. There were 24 patients with fluid responsiveness (14 males and 10 females; R group) and 20 with non-responsiveness (9 males and 11 females; NR group). There were no significant differences in the age, gender, HR, BP, dosages of vasopressors, acute physiology and chronic health evaluation score, and BMI between R group and NR group (Table 1).

3.2. Hemodynamic parameters before and after fluid boluses (Table 2)

After fluid boluses, the MAP, CVP and CI in both groups increased significantly ($P < .05$), and the HR, ΔSVV , and ΔPPV dramatically reduced as compared to those before fluid boluses ($P < .05$). In addition, there were marked differences in these parameters between 2 groups ($P < .05$).

3.3. Correlations among ΔSVV , ΔPPV , ΔCI , and ΔVTI (Figs. 3–5)

ΔSVV , ΔPPV , and ΔCI had positive relationships with ΔVTI ($r = 0.529$, $P < .001$; $r = 0.4$, $P = .03$; $r = 0.717$, $P < .001$).

3.4. Prediction of fluid responsiveness with ΔSVV , ΔPPV , ΔVTI and ΔCVP (Fig. 6, Table 3)

If the cutoff value was 24.8%, the sensitivity, specificity, AUC and 95% CI of ΔSVV were 66.7%, 95%, 0.800, and 0.660 to

0.940, respectively, in the prediction of fluid responsiveness. If the cutoff value was 25.8%, the sensitivity, specificity, AUC and 95% CI of ΔPPV were 83.3%, 75%, 0.843, and 0.729–0.956, respectively, in the prediction of fluid responsiveness. The AUC of ΔVTI was 0.956, which was larger than those of ΔSVV and ΔPPV . If the cutoff value was 15.9%, the sensitivity and specificity of ΔVTI was 87.5% and 95%, respectively, in the prediction of fluid responsiveness. ΔCVP failed to predict fluid responsiveness in these patients..

4. Discussion

In the septic shock patients, our results showed the CI increased by $\geq 15\%$ in responsive patients and by $< 15\%$ in non-responsive patients after VET. The SVV and PPV after VET were significantly different between responsive and non-responsive groups. In addition, ΔSVV , ΔPPV , and ΔCI were positively related to ΔVTI . SVV, PPV, and $\Delta\text{VTI}_{\text{LVOT}}$ could be used to predict the fluid responsiveness (AUC = 0.80, 0.843, and 0.956, respectively), with $\Delta\text{VTI}_{\text{LVOT}}$ having the best predictive performance.

In the present study, the PPV and SVV of PiCCO parameters were used as the “gold standard” to assess the ΔVTI in combination with the PiCCO parameters after fluid bolus. In the present study, rapid fluid bolus was administered (500ml of saline was administered within 15 minute). Our results showed that the static hemodynamic parameters changed significantly in both R group and NR group ($P < .05$), although there were marked differences between 2 groups. Thus, the changes in above parameters may not reflect the fluid responsiveness and thus active fluid supplement based on these parameters might cause volume overload. These parameters have limited roles in guiding fluid resuscitation. The ROC analysis also showed that ΔCVP had no predictive value for fluid responsiveness.

In addition, the PiCCO parameters (ΔSVV , ΔPPV , and CI) were related to the ΔVTI on color Doppler ultrasonography ($r = 0.529$, 0.4, and 0.717, respectively). ΔSVV and ΔPPV are the dynamic parameters based on the cardiopulmonary interaction and have favorable value in clinical practice as shown a variety of studies. In addition, ΔVTI had a predictive value for fluid responsiveness.

In this study, patients received complete sedation and mechanical ventilation with a relatively high tidal volume of 8 to 10 ml/kg. Diseases, such as arrhythmia and heart valve disease with regurgitation, were excluded in patients enrolled for PiCCO. Thus, in patients with acute respiratory distress syndrome receiving mechanical ventilation at a low tidal volume, more studies are needed to confirm the relationship between ΔVTI and PiCCO.

Of note, the correlation coefficient of ΔVTI and CI was 0.717, suggesting the close relationship between ΔVTI and CI, but they did not increase proportionally. In the assessment of left ventricular function, SV is calculated as follow: $\text{SV} = \text{VTI}_{\text{LVOT}}$

Table 2
Routine hemodynamical parameters before and after fluid boluses in patients of 2 groups.

Group	n	HR (beats/min)			MAP (mm Hg)			CVP (cmH ₂ O)		
		Before	After	t	Before	After	t	Before	After	t
R	24	120.87 ± 8.72	112.0 ± 8.76	8.04*	62.33 ± 4.6	75.95 ± 5.6	-14.18*	8.04 ± 4.42	11.16 ± 4.27	-7.7*
NR	20	121.91 ± 9.63	117.2 ± 8.87†	8.30*	61.85 ± 6.8	65.55 ± 5.8†	-7.74*	9.50 ± 4.23	15.72 ± 3.22†	-15.5*

R=fluid responsiveness, NR=no fluid responsiveness.

* $P < .05$, compared between before and after fluid boluses.

† $P < .05$, compared between R and NR group.

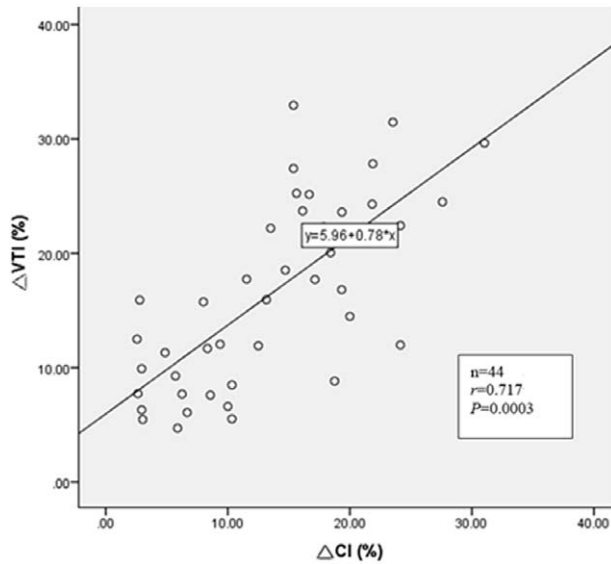


Figure 3. Correlation between stroke volume variation in pulse index continuous cardiac output parameters and left ventricular outflow tract time rate time integral on chest color doppler ultrasonography. Notes: ΔSVV =stroke volume variation, ΔVTI =left ventricular outflow tract time rate time integral.

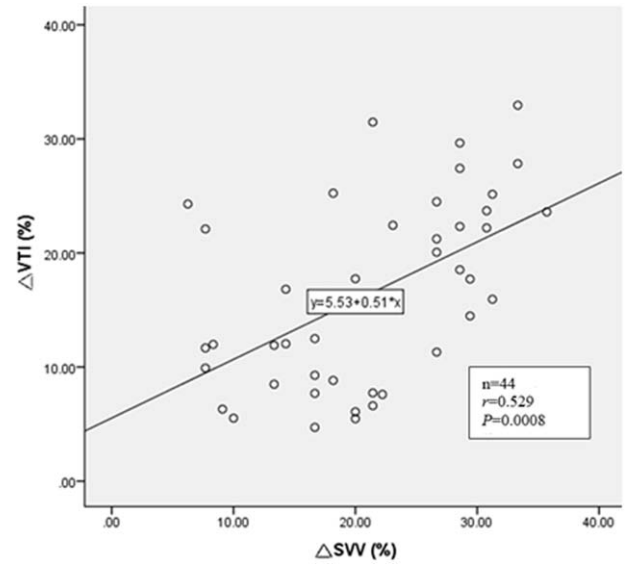


Figure 5. Correlation between cardiac index in pulse index continuous cardiac output parameters and left ventricular outflow tract time rate time integral on chest color doppler ultrasonography. Notes: ΔCI =cardiac index, ΔVTI =left ventricular outflow tract time rate time integral.

$\times (D_{LVOT}/2)^2 \times \pi \times HR$. Chauvet et al found that about 22% of patients with sepsis had functional LVOT obstruction (LVOTO), and fluid resuscitation could improve LVOTO,^[15] suggesting the dynamic change in the diameter of LVOT. The present study also showed HR also changed dynamically after fluid resuscitation, which means that the change in SV is uncertain during the fluid resuscitation. Therefore, the cardiac output determined by color doppler ultrasonography is often overestimated in patients with sepsis, and the disproportional change between VTI and CI is

objective. As compared to the changes in cardiac output and CI, ΔVTI_{LVOT} is measured in clinical practice to reflect changes in cardiac output, which is relatively easy to measure and warranted to be promoted in clinical practice.

The predictive power of each indicator was further evaluated by the corresponding ROC curve. Our results showed the sensitivity and specificity were 66.7% and 95%, respectively, for ΔSVV , and 83.3% and 75%, respectively, for ΔPPV . These findings were consistent with previously reported. The AUC of ΔVTI_{LVOT} was 0.956 (95% CI was 0.902–1.000), and the

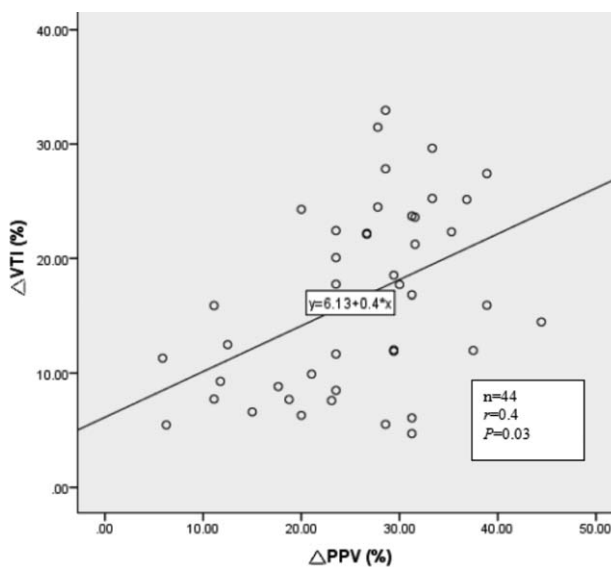


Figure 4. Correlation between pulse pressure variation in pulse index continuous cardiac output parameters and left ventricular outflow tract time rate time integral on chest color doppler ultrasonography. Notes: ΔPPV =pulse pressure variation, ΔVTI =left ventricular outflow tract time rate time integral.

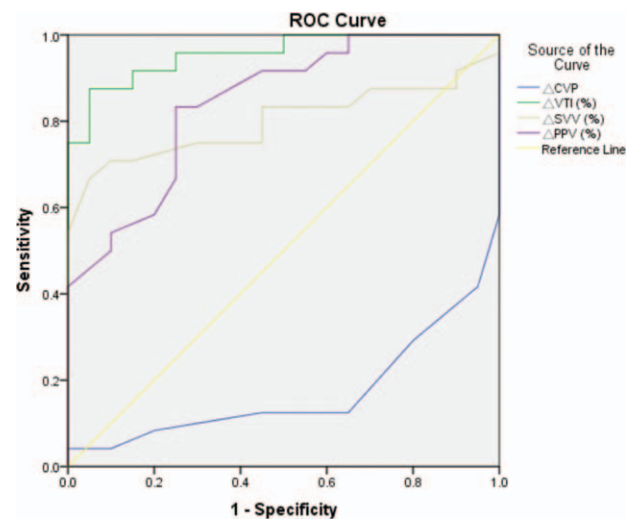


Figure 6. ROC curves of Δ stroke volume variation, Δ pulse pressure variation, Δ central venous pressure and Δ left ventricular outflow tract time rate time integral in the prediction of fluid responsiveness of septic shock patients. Notes: ΔCVP =central venous pressure, ΔPPV =pulse pressure variation, ΔSVV =stroke volume variation, ΔVTI =left ventricular outflow tract time rate time integral.

Table 3**Predictive value of Δ left ventricular outflow tract time rate time integral, Δ stroke volume variation and Δ pulse pressure variation in fluid responsiveness.**

Parameters	Cutoff	AUC	95%CI	Sensitivity (%)	Specificity (%)
Δ VTI (%)	15.9	0.956	0.902–1.000	87.5	95
Δ SVV (%)	24.8	0.800	0.660–0.940	66.7	95
Δ PPV (%)	25.8	0.843	0.729–0.956	83.3	75

AUC=area under the receiver operating characteristic curve, Δ PPV=pulse pressure variation, Δ SVV=stroke volume variation, Δ VTI=left ventricular outflow tract time rate time integral.

sensitivity and specificity was 87.5% and 95%, respectively. This suggests that Δ VTI_{LVO_T} is better to other invasive parameters in the assessment of fluid responsiveness. The bedside color doppler ultrasonography is non-invasive, can be performed repeatedly, and is less costly, suggesting a good prospect in clinical application.

4.1. Limitations

This was not a double-blind, randomized study. In addition, all the patients received sedation and mechanical ventilation. Thus, whether these findings are also applicable in patients with spontaneous breathing receiving mechanical ventilation should be further investigated. VTI_{LVO_T} may predict the fluid responsiveness and avoid volume overload. However, it doesn't mean that the patients actually need the fluid supplement. In addition, the relationship between volume overload and prognosis was not discussed. VTI_{LVO_T} mainly reflects the left ventricular function, and the factors affecting the right ventricular dysfunction were not investigated. The sample size was small, and more multi-centered clinical studies with large sample size are needed to confirm our findings.

In conclusion, in the volume management of patients with septic shock, proper fluid resuscitation is one of the important measures to improve the success rate of treatment. VTI_{LVO_T} has a high predictive value for fluid responsiveness. With the wide application of bedside ultrasound in clinical practice, color doppler ultrasonography may serve as a safe, non-invasive, repeatable tool in the assessment of fluid status and fluid responsiveness, which may guide the clinical volume management.

Author contributions

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