Original Article
The benefits of a variable SVV threshold using cardiopulmonary ultrasound to guide perioperative fluid therapy in patients with ARDS

Kai Wang[1,2*], Bo-Xiang Du[3*], Yan Zhang[1,2*], Xiang Huan[1,2], Yu-Lei Qiu[4], Chao Chen[4], Li-Wei Wang[1,2]

[1]Department of Anesthesiology, Xuzhou Central Hospital, Xuzhou, Jiangsu, China; [2]Affiliated Hospital of Nanjing Medical University, Xuzhou, Jiangsu, China; [3]Department of Anesthesiology, The Second Affiliated Hospital of Nantong University, Jiangsu, China; [4]Suzhou Vocational Health College, Jiangsu, China. *Equal contributors.

Abstract: Purpose: We aimed to explore the advantages of a variable stroke volume variation (SVV) threshold using cardiopulmonary ultrasound in perioperative fluid therapy for patients with ARDS caused by severe craniocerebral trauma. Methods: One hundred emergency surgery patients were enrolled in this clinical trial and randomly divided into a control group and a test group. At the beginning, the threshold of fluid therapy was SVV > 13%, and 8 ml/kg of Ringer's lactate was given within 20 minutes. A change in the cardiac index (ΔCI) above 15% was defined as effective. If the ΔCI was < 15% after the fluid challenge, it was regarded as ineffective, and the threshold was changed to SVV > 15% in the subsequent treatment in the test group. MAP, SPO_2, HR, PaO_2/FiO_2, the inferior vena cava respiratory collapsibility index (IVC-CI), CI, and the lung B-line scores were recorded before and after therapy. The patients were also followed up in the ICU. Results: Seventy-nine patients were enrolled in the study. In the test group, less fluid was administered during the operation (2230±412 ml vs 2834±381 ml) with a higher threshold of SVV (14.8±0.8 vs 13.1±0.2), the mechanical ventilation time was shorter (13.2±3.19 days vs 15.1±3.27 days), with higher PaO_2/FiO_2 in the ICU compared with the control group (P < 0.05). There were no statistical differences in the other outcomes. The ROC curve suggests that the SVV (sensitivity: 92.55%, specificity: 72.35%) and the IVC-CI (sensitivity: 92.55%, specificity: 63.13%) can predict fluid responsiveness well, and the best cut-offs were SVV ≥ 13.5% and IVC-CI ≥ 31.16%. Conclusions: The variable SVV threshold was of greater benefit for guiding perioperative fluid therapy in patients with ARDS caused by severe craniocerebral trauma, and cardiopulmonary ultrasound can successfully evaluate which is superior.

Keywords: Fluid therapy, stroke variability index, inferior vena cava respiratory attenuation index, cardiopulmonary ultrasound, ARDS

Introduction

Patients who suffer severe traumatic brain injury often experience acute respiratory distress syndrome (ARDS) due to the severe trauma, increased intracranial pressure, shock, infection, hypoxia, and aspiration pneumonia [1-3]. Hemodynamic instability is a complication for these patients. Fluid resuscitation is the primary treatment in the perioperative period [4]. A sufficient volume of circulating blood is essential to provide a good cardiac output and ensure tissue perfusion. However, improper fluid therapy will lead to excess blood volume, which produces serious complications such as tissue hypoxia, lactic acid accumulation, pulmonary

edema, and directly affects the prognoses of the patients [4, 5]. Therefore, it is important to conduct a reasonable goal-directed therapy (GDT) in a scientific and effective manner to accurately assess each patient's volume status. Previous studies have indicated that in order to reduce brain edema after damage to the nervous system, tight fluid control is necessary while maintaining circulation stability [6]. For patients with ARDS, this is even more difficult. High-permeability pulmonary edema caused by alveolar and capillary endothelial cell injury is the basic pathophysiological feature of ARDS. Excess fluid will aggravate pulmonary edema, prolong postoperative mechanical ventilation, and increase the incidence of complica-

tions and mortality. As a result, a more cautious and tight fluid control is needed for this complex situation. However, no study has been conducted to explore how to manage fluid therapy or establish which parameter is the best predictor of fluid responsiveness.

Stroke volume variation (SVV), which is based on the Vigileo system, has been widely used in recent years to guide fluid therapy and predict the volume response, with good sensitivity and specificity [7]. Willars found that SVV was an adequate predictor of fluid responsiveness in high-risk vascular surgical patients [8]. Yang demonstrated that SVV is a sensitive predictor of fluid responsiveness in patients before brain surgery [9]. However, this method also has certain limitations. With different types of patients, and different hemodynamic targets, the threshold of SVV > 13% as the fluid challenge cannot be used easily. In addition, owing to measurement deviation, SVV sometimes has a poor correlation with gold indicator cardiac index (CI) changes, which may result in excessive or insufficient fluid infusion [10, 11].

Cardiopulmonary combined ultrasound is a new method that measures CI, the inferior vena cava collapsibility index (IVC-CI), and the lung B-line score to guide fluid therapy. It has been proven to improve the prognosis of patients with ARDS and septic shock in intensive care units (ICUs) [12-14]. This monitoring method requires an expert in ultrasound and cannot be continuously measured, so is hard to use in routine operations. However, it is very useful for evaluating the patients' fluid volume statuses and correcting the SVV measurement results [15].

The aim of this study was to improve the precision of fluid intake for patients with severe brain trauma and ARDS using the variable SVV threshold during operations and to assess the accuracy of SVV measurement using cardiopulmonary ultrasound. Additionally, the hemodynamic parameters were also pooled to evaluate the power of the prediction of fluid responsiveness in order to exert their respective advantages and explore the optimal treatment options in the future.

Materials and methods

This was a randomized, controlled trial that compared using fixed SVV alone with variable SVV as the predictor to guide fluid therapy during surgery. The trial was approved by the ethics committee of the Central Hospital of Xuzhou, Nanjing Medical University, and registered in the Chinese Clinical Trial Registry (approval number: ChiCTR1900026664).

Patient population

One hundred patients with severe craniocerebral trauma combined with ARDS who underwent a craniotomy for hematoma evacuation in Xuzhou Central Hospital from January 2017 to September 2018 were enrolled in this trial. Before the operation was carried out, the patients' legal representatives were asked to sign informed consents. The inclusion criteria were: Age > 18 years; patients with severe traumatic brain injury combined with ARDS treated with craniotomy and hematoma evacuation. ARDS was defined using the Berlin Definition: 1) Timing: within one week of a known clinical insult, or new or worsening respiratory symptoms. 2) Chest imaging: bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules. 3) Origin of edema: respiratory failure not fully explained by cardiac failure or fluid overload, needing objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor was present. 4) Oxygenation: mild, 200 mmHg < PaO_2/F_iO_2 ≤ 300 mmHg with PEEP or CPAP ≥5 cmH_2O; Moderate, 100 mmHg < PaO_2/F_iO_2 ≤ 200 mmHg with PEEP ≥ 5 cmH_2O; Severe, PaO_2/F_iO_2 ≤ 100 mmHg with PEEP ≥ 5 cmH_2O. The exclusion criteria were: Any contraindication to fluid challenge, such as congestive heart failure or evidence of fluid overload; pregnant women; patients who suffered a cerebrovascular accident; conditions which could affect SVV and cardiopulmonary ultrasound measures, such as pneumothorax, arrhythmia, or abdomen visceral rupture.

Randomization, allocation, and blinding

The computer-generated sequences method was used for the randomization. Allocation envelopes were prepared and sequentially assigned to the consenting patients in the operating room before the induction. The envelopes were opened by the anesthesiologists who were responsible for the intraoperative care. After that, the patients were enrolled in either the control group (with only SVV > 13% as the

threshold of fluid challenge), or the test group (with variable thresholds of SVV > 13% or SVV > 15%). The attending anesthesiologists managed the fluid therapy according to the protocol of each group. All of the surgical, nursing and ICU teams were blinded to the patients' assignments. The outcome data were adjudicated by the principal investigator (LW.W), who was also blinded to the patients' allocations.

Study protocol

When the patients entered the operating room, the Glasgow coma scale (GCS) was used to assess their nervous system status. Electrocardiography, the heart rate (HR), the pulse oxygen saturation (SpO_2), the oxygenation index (PaO_2/F_iO_2), and the invasive arterial blood pressure were monitored. Anesthesia was induced with midazolam (0.04 mg/kg), etomidate (0.3 mg/kg), sufentanil (5 ug/kg), and cisatracurium (0.2 mg/kg). The ventilation mode was volume-controlled, and the tidal volume was 6 ml/kg, 12 times per minute, PEEP 5 cmH_2O. During the operation, 4 mg/kg/h of propofol and 0.3 ug/kg/min of remifentanil were used to maintain the anesthesia. The nasopharyngeal temperature was maintained at 36-37°C with forced-air warming blankets. SVV and CI were monitored via a Vigileo monitor (Edwards Lifesciences, USA). A 7.5 F dual-chamber central venous catheter was inserted in the right internal jugular vein to monitor CVP. The left ventricular ejection fraction (LVEF), IVC-CI, and the lung B-line scores were measured using ultrasound.

At the beginning, the threshold of fluid challenge was SVV > 13% in both groups and 8 ml/kg Ringer's lactate was infused within 20 minutes. According to other studies, patients who showed an increase in CI (ΔCI) of ≥ 15% were categorized as responders for fluid challenge [1, 16]. Those with SVV > 13% but ΔCI < 15% were categorized as non-responders, which meant that fluid infusion was unnecessary and may have caused fluid overload, inducing the aggravation of brain edema and ARDS. Therefore, in the test group the subsequent threshold was modified to SVV > 15%, but there was no change in the control group (**Figure 1**). A continuous infusion of 0.5 ml/kg/h of crystalloid solution was run throughout the case. Colloid (succinylated gelatin) and blood products were also used during the operation, depending on the patients' statuses. If the

hemoglobin (Hb) in the peripheral blood was lower than 70 mg/L, a red blood cell suspension was infused. When the CI was < 2.0 L/min/m² and the SVV was < 10%, indicating impaired cardiac function, 2-20 ug/kg/min dopamine or dobutamine was used for the anti-shock treatment. The values of mean arterial pressure (MAP), SpO_2, HR, PaO_2/F_iO_2, LVEF, CI, IVC-CI, and the lung B-line score were recorded before and after each fluid challenge. When each operation ended, the average fluid challenge duration, the total infusion volume, and the blood lactate level (Lac) were recorded for analysis.

After the operation, the patients were transferred to the ICU and received the usual standard of care. The postoperative fluid management (decided by the attending doctors) was the same for both groups and was based on the patients' cardiopulmonary functions. The suggested hemodynamic target values were CVP 8-10 mmHg, and MAP 70-80 mmHg. The outcomes of serum tumor necrosis factor alpha (TNF-α), interleukin 6 and 10 (IL-6 and IL-10), C-reverse protein (CRP) and cortisol (COR) concentration at 24 hours (D_1) and 48 hours (D_2) after the operation were recorded and compared with the values before the operation (D_0). The average serum creatinine (Cr) and blood urea nitrogen (BUN) levels in the ICU, the duration of the mechanical ventilation and the stay in the ICU and 30-day mortality were explored. The Glasgow outcome scale (GOS) was used to evaluate the nervous system status when the patients were discharged from the hospital (GOS: 5, good recovery; 4, moderate disability; 3, severe disability; 2, persistent vegetative state; 1, death) [17].

Ultrasound technology

An ALOKA (Hitachi Aloka Medical) Prosound F75 ultrasound machine with a 3.5-5 MHz probe was used for the evaluation. The LVEF was calculated by the biplane Simpson's method, and the parasternal left ventricular long axis section or standard apical four chamber section was located. The left ventricular end-diastolic volumes (LVEDVs) were measured when the ventricular cavity expanded to the maximum, and the left ventricular end-systolic volumes (LVESV) were measured when the ventricular cavity retracted to the minimum. The shapes of the ventricular cavity were drawn along the left ventricular endocardium, and the
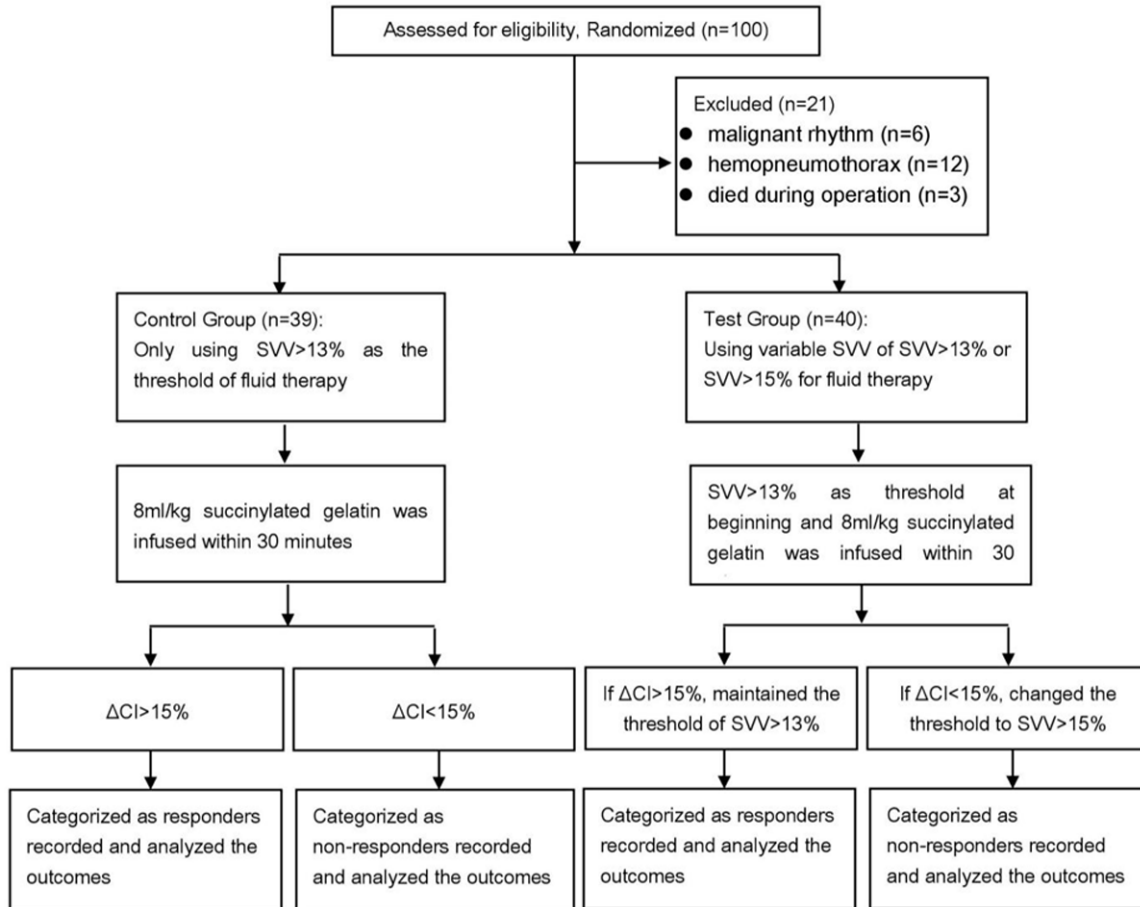
Figure 1. CONSORT diagram of patient flow through the study.

values were the means of three consecutive measures. LVEF was calculated as: LVEF = [(LVEDV-LVESV)/LVEDV] × 100%.

IVC-CI was calculated by detecting the inferior vena cava behind the liver. The diameter of the inferior vena cava was measured at the 2 cm position before the junction of the superior hepatic vein and the inferior vena cava. The M mode was used to collect the IVC change for ten seconds (including two/three breath cycles). The maximum diameter (IVC_{max}) and the minimum diameter (IVC_{min}) were measured three times, and the average was calculated. The IVC-CI was calculated as IVC-CI = [(IVC_{max}-IVC_{min})/IVC_{max}] × 100%.

The lungs were divided into upper and lower regions through the sternal angle horizontal line, and then each region was divided into three parts: the front, the middle and the back, using the front and posterior axillary line as the boundary and, ultimately, 12 areas were divid-

ed. Each area was detected and the most severe abnormality was characterized with this area. The scores were defined as: normal (0 points): one line or two independent B lines; moderate reduction of lung inflation (1 point): multiple obvious and distinguishable B lines, the distance between adjacent B lines ≤ 7 mm; lung inflation severely reduced (2 points): multiple B lines fused together, the distance between adjacent B lines ≤ 3 mm; Lung consolidation (3 points): the lungs showed a tissue-like change with dynamic bronchial aeration. The final total lung scores were the sum of all the 12 regions [18]. All of the ultrasound measurements and data collection were performed by the same experienced sonographer who was blinded to the patients' assignments.

Statistical analysis

The statistical analysis was performed using SPSS 16.0 statistical software. All measurement data were tested for a normal distribution

Table 1. Patient demographics and baseline characteristics

	Control group (n=39)	Test group (n=40)	P value
Age (years)	45.1 (8.1)	43.0 (7.2)	0.267
Gender (male/female)	28/11	30/10	0.803
BMI (kg/m^2)	22.4 (4.9)	22.2 (4.7)	0.854
ASA III	30 (76.9%)	31 (77.5%)	0.999
ASA IV	9 (23.1%)	9 (22.5%)	0.999
GCS	5.7 (1.9)	5.5 (1.8)	0.632
PaO$_2$/FiO$_2$	179.5 (32.1)	171.8 (26.7)	0.293
MAP (mmHg)	119.2 (12.2)	116.2 (10.2)	0.282
HR (bpm)	105.8 (11.2)	107.8 (8.8)	0.423
CVP (cmH$_2$O)	11.4 (2.7)	11.3 (2.4)	0.872
SVV (%)	12.0 (2.4)	12.3 (2.1)	0.592
CI (L/min.m^2)	3.03 (0.2)	3.1 (0.3)	0.285
IVC-CI (%)	37.6 (11.4)	35.1 (8.3)	0.315
Lac (mmol/L)	2.4 (1.7)	2.3 (1.7)	0.812
Lung B-line score	14.7 (3.6)	14.5 (3.9)	0.825

Continuous variables are presented as the means (standard deviation); ASA = American Society of Anesthesiologists; BMI = body mass index; GCS = Glasgow coma scale; MAP = mean arterial pressure; HR = heart rate; bpm = beats per minute; CVP = central venous pressure; SVV = stroke volume variation; CI = cardiac index; IVC-CI = inferior vena cava collapsibility index; Lac = Lactic acid.

and expressed as the mean ± standard deviation (x ± s). The hemodynamic data before and after the fluid therapy in the group were analyzed using paired t-tests, and one-way ANOVA was used for the comparisons of the data between groups. Chi-squared (χ^2) tests were used for the counting data. The predictive values of the measured parameters (SVV, IVC-CI, CI, CVP, MAP and HR) for the fluid challenge were evaluated using a receiver operating characteristic (ROC) curve analysis, and presented as the area under the curve (AUC) with 95% confidence intervals. $P < 0.05$ was considered statistically significant.

Results

Out of 100 patients, 21 were excluded as 6 had unstable rhythm, 12 had hemopneumothorax, and 3 died during the operation. A total of 79 patients were enrolled in the study, aged 30-60 (44.1±7.56) years, ASA III-IV grade, with a body mass index (BMI) of 22.3±4.8 kg/m^2. There were 39 patients in the control group and 40 in the test group. The GCS of all the patients was under 8, which indicated severe craniocerebral trauma. The PaO$_2$/F$_i$O$_2$ was under 300 mmHg

without any obvious cardiac insufficiency, and the lung B-line score was also higher than normal, which can be defined as ARDS according to the Berlin Definition. There were no significant differences in the demographics or baseline characteristics between the two groups ($P > 0.05$) (**Table 1**).

The comparison of the outcomes before and after the fluid challenge

Because a variable threshold of SVV was used in the test group, the SVV in the test group (14.8±0.8) was significantly higher than it was in the control group (13.1±0.2) ($P < 0.05$). After the fluid challenge, the SVV and the IVC-CI were significantly decreased, and there was a difference between the two groups - SVV: 11.9±1.5 *vs* 11.1±1.1; IVC-CI: 32.9±5.8 *vs* 30.1±5.4, respectively ($P < 0.05$). The CI was significantly elevated after the fluid challenge in both groups, and the increase in CI (ΔCI) was 16.6±3.3 in the test group and 14.1±2.7 in the control group, with a significant difference ($P < 0.05$). Compared with the other variables, HR was significantly decreased after the fluid challenge ($P < 0.05$); however, the MAP and CVP had no significant differences before or after the fluid challenge ($P > 0.05$) (**Table 2**).

Comparison of the outcomes after operation

At the end of the operation, all of the data were summarized and compared between the two groups. In our study, the total number of fluid challenges was 142 (3.55±0.9 times in each patient) in the test group, and among them there were 78 with a threshold of SVV > 15%. In the control group, there were a total of 170 fluid challenges (4.36±1.1 in each patient, $P < 0.05$). During the operation, the total fluid administration (2230±412 ml *vs* 2834±381 ml) and Ringer's lactate intake (1684±512 ml *vs* 2209±438 ml) were less in the test group compared with the control group ($P < 0.05$). The lung B-line score was also lower (15.8±3.96 *vs* 18.7±4.37), and the PaO$_2$/FiO$_2$ was higher in the test group (172.3±26.7 *vs* 154.4±28.5) compared with the control group ($P < 0.05$). There was no difference in outcome for succinylated gelatin, blood-products intake, operation and anesthesia time, blood loss, urine volume, vasoactive

Table 2. Comparison of the outcomes before and after the fluid challenges

	Control group (n=39)	Test group (n=40)	P value
SVV (%)			
Before	13.1 (0.2)	14.8 (0.8)	< 0.001
After	11.1 (1.1)*	11.9 (1.5)*	0.009
CI (L/min.m²)			
Before	3.2 (0.4)	3 (0.6)	0.086
After	3.5 (0.5)*	3.4 (0.5)*	0.377
ΔCI (%)	14.1 (2.7)	16.6 (3.3)	< 0.001
IVC-CI (%)			
Before	32.9 (6.8)	36.1 (5.7)	0.026
After	30.1 (5.4)*	32.9 (5.8)*	0.029
CVP (cmH$_2$O)			
Before	10.3 (2.1)	10.1 (2.7)	0.715
After	11.8 (2.9)	11.1 (3.1)	0.304
MAP (mmHg)			
Before	99.8 (10.7)	98.7 (11.6)	0.663
After	102.3 (10.8)	100.7 (12.9)	0.552
HR (bpm)			
Before	98.1 (7.6)	100.1 (8.2)	0.265
After	93.4 (8.1)*	95.7 (8.9)*	0.224

Continuous variables are presented as the means (standard deviation); SVV = stroke volume variation; CI = cardiac index; ΔCI = the variety of the cardiac index before and after the fluid challenge; IVC-CI = inferior vena cava collapsibility index; CVP = central venous pressure; MAP = mean arterial pressure; HR = heart rate; bpm = beats per minute. *A significant difference between before and after the fluid challenge within the group, $P < 0.05$.

agents use, LVEF, or Lac, between the two groups ($P > 0.05$) (**Table 3**).

Comparison of the outcomes in ICU

There were no significant differences in postoperative fluid management, the use of vasoactive agents, or other usual standards of care in the ICU between the two groups. The patients in the test group had shorter mechanical ventilation times (9.8±2.76 days *vs* 11.7±2.33 days), and lower ICU admission times (13.2±3.19 days *vs* 15.1±3.27 days), respectively ($P < 0.05$). The PaO$_2$/FiO$_2$ level was followed-up for 12 days after the operation, and the value was still lower than 300 in the first 5 days in the test group, and the first 8 days in the control group. Between the two groups, PaO$_2$/FiO$_2$ was higher in the test group from D$_2$ to D$_{11}$ ($P < 0.05$) (**Figure 2**). The levels of CRP, COR, TNF-α, IL-6 and IL-10 were significantly higher at D$_1$ and D$_2$

than at D$_0$ in each group ($P < 0.05$). Between the two groups, the TNF-α was lower at D$_1$, and IL-10 was higher at D$_2$ in the test group ($P < 0.05$). Comparing the outcomes of Lac, Cr, BUN, GOS and death in ICU, no statistical difference was found ($P > 0.05$) (**Table 4**).

ROC analysis for prediction of fluid responsiveness

The endpoints of SVV, IVC-CI, CI, CVP, MAP and HR were pooled to evaluate the prediction of fluid responsiveness by ROC analysis. The highest value of AUC was 0.853 in IVC-CI and the best cut-off was 34.98% (sensitivity: 92.55% and specificity: 63.13%); the AUC for SVV was 0.831 and the best cut-off was 13.5% (sensitivity: 92.55% and specificity: 72.35%); the AUC for CI was 0.666 and the best cut-off was 2.95 L/min.m² (sensitivity: 32.98% and specificity: 97.24%); the AUC for CVP was 0.611 and the best cut-off was 10.5 cmH$_2$O (sensitivity: 57.45% and specificity: 61.29%); the AUC for MAP was 0.578 and the best cut-off was 96.5 mmHg (sensitivity: 80.85% and specificity: 39.17%); the AUC for HR was 0.511 and the best cut-off was 104.5 bpm (sensitivity: 87.23% and specificity: 27.65%) (**Table 5**; **Figure 3**).

Discussion

Patients with severe craniocerebral trauma combined with ARDS have a high risk of perioperative mortality. Owing to the craniocerebral injury and increased intracranial pressure, the sympathetic-adrenalin axis is over activated, and, consequently, neurogenic pulmonary edema and hypoxemia appear. The release of various cytokine factors aggravate the inflammatory response and generate systemic inflammatory response syndrome (SIRS). The alveolar and capillary endothelial cells are damaged, and permeability is increased, which results in ARDS. Additionally, hemopneumothorax, pulmonary contusion, vomiting, and aspiration after coma are also important causes of pulmonary inflammation, pulmonary edema and hypoxemia. As for these complex situations, we need to immediately take effective measures to maintain the perfusion of important organs. On the other hand, we should also consider the state of cerebral and pulmonary edema and conduct reasonable and effective fluid therapy. The key is to improve the patients' prognoses.

Table 3. Comparison of the outcomes after the operations

	Control group (n=39)	Test group (n=40)	P value
Total infusion volume (ml)	2834 (381)	2230 (412)	< 0.001
Ringer's lactate	2209 (438)	1684 (512)	< 0.001
succinylated gelatin	326 (162)	359 (178)	0.025
blood products	314 (208)	298 (192)	0.723
Fluid challenge time (n)	4.36 (1.1)	3.55 (0.9)	0.002
PaO_2/FiO_2	154.4 (28.5)	172.3 (26.7)	0.009
Lung B-line score	18.7 (4.7)	15.4 (3.9)	0.003
Operation time (h)	2.48 (0.5)	2.53 (0.7)	0.723
Anesthesia time (h)	2.69 (0.5)	2.72 (0.7)	0.838
Blood loss (ml)	645 (89)	671 (101)	0.229
Vasoactive agents use (n)	8 (20.5%)	9 (22.5%)	0.642
Urine (ml)	359 (67)	332 (58)	0.059
LVEF (%)	54 (6)	53 (5)	0.423
Lac (mmol/L)	2.4 (1.4)	2.5 (1.3)	0.758

Continuous variables are presented as the means (standard deviation); LVEF = Left ventricular ejection fraction; Lac = Blood lactic acid.
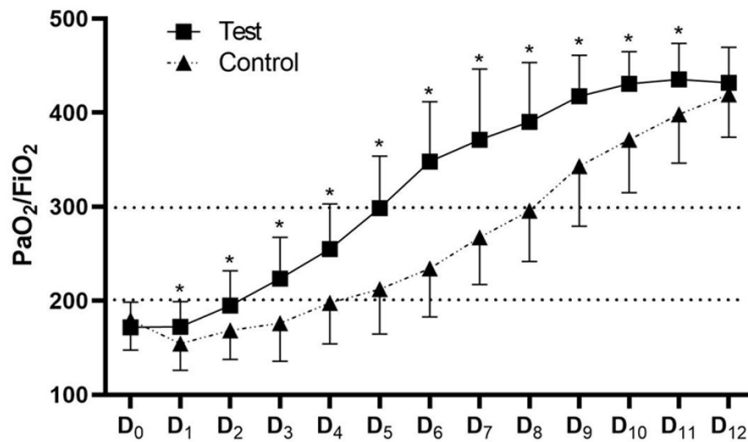

Figure 2. Comparisons of the PaO_2/FiO_2 levels at different time points between the two groups. D_0 = baseline before the operation; D_1-D_{12} = 1-12 days after the operation. All values represent the means ± standard deviation. *P < 0.05, the test group vs the control group.

ent's pathophysiological condition will affect the outcomes and result in inconsistent true values. Cardiopulmonary ultrasonography can directly reflect the cardiovascular statement by measuring the inferior vena cava variability, cardiac ejection, and pulmonary conditions. But the operation is relatively complicated and cannot be continuously measured.

The purpose of this study was to explore whether the two combined methods could better guide the fluid therapy of high-risk patients. The results showed that the perioperative total fluid intake was significantly lower in the test group and had no statistical difference in the outcomes of MAP, CVP, CI, Lac, Cr, and BUN between the two groups. Additionally, the lung B-line score was lower in the test group, which indicated that lower fluid intake can successfully maintain hemodynamic stability and the perfusion of important organs. On the other hand, an excess of fluid intake in the control group was probably the reason for postoperative pulmonary edema and prolonged ICU mechanical ventilation.

The highlight of our study was using the variable SVV threshold for fluid therapy during the operation, and the procedure was corrected by cardiopulmonary ultrasound. We analyzed the threshold of each fluid challenge in the test group and determined that if the changes of SVV were inconsistent with ΔCI, the threshold was not correct. Therefore, in the subsequent tests, the threshold would be adjusted to a stricter level to avoid unnecessary fluid input.

The Vigileo system and cardiopulmonary ultrasonography are currently widely used to guide fluid therapy. It has been reported that Vigileo and cardiopulmonary ultrasonography can be used successfully in patients with septic shock [13], traumatic brain injury [4], thoracic surgery [11], and has advantages over traditional methods in both perioperation and ICU. However, some deficiencies should also be considered. The Vigileo system estimates the data that is obtained from the peripheral arterial. The choice of puncture position, the adjustment of the mechanical ventilation method, and the pati-

In the test group, 142 fluid challenges were performed with 40 patients; 78 of which were adjusted to the threshold of SVV > 15%. The

Table 4. Comparison of the outcomes in the ICU

	Control group (n=39)	Test group (n=40)	P value
CRP (mg/L)			
D_0	5.3 (1.4)	5.2 (1.3)	0.743
D_1	20.7 (7.2)*	18.9 (8.3)*	0.307
D_2	32.9 (9.6)*	30.5 (10.4)*	0.290
COR (nmol/L)			
D_0	291.6 (49.0)	290.6 (47.2)	0.927
D_1	317.3 (48.2)*	330.5 (70.6)*	0.336
D_2	332.6 (47.6)*	323.5 (76.7)*	0.530
TNF-α (pg/ml)			
D_0	66.3 (3.5)	60.6 (4.7)	0.749
D_1	88.9 (20.7)*	72.4 (17.3)*	< 0.001
D_2	144.5 (30.8)*	135.7 (48.5)*	0.340
IL-6 (pg/ml)			
D_0	55.5 (18.2)	60.5 (20.2)	0.252
D_1	78.9 (21.5)*	88.3 (26.6)*	0.089
D_2	92.1 (32.6)*	86.7 (24.3)*	0.406
IL-10 (pg/ml)			
D_0	10.8 (3.5)	9.6 (4.5)	0.191
D_1	19.6 (7.5)*	22.5 (8.7)*	0.117
D_2	34.4 (14.6)*	48.1 (13.5)*	< 0.001
Cr (umol/L)	97.5 (14.6)	100.1 (16.4)	0.490
BUN (mmol/L)	5.3 (0.9)	5.4 (0.8)	0.624
MV time (day)	11.7 (2.3)	9.8 (2.7)	0.003
Stay in ICU (days)	15.1 (3.3)	13.2 (3.2)	0.018
GOS	3.5 (0.8)	3.6 (0.9)	0.821
Death (n)	5 (12.8%)	3 (7.5%)	0.378

Continuous variables are presented as the means (standard deviation); CRP = C-reactive protein; COR = cortisol; TNF-α = tumor necrosis factor α; IL-6 = interleukin 6; IL-10 = interleukin 10; D_0 = before the operation; D_1 = the first day after the operation; D_2 = the second day after the operation; Cr = serum creatinine; BUN = blood urea nitrogen; MV time = mechanical ventilation time; GOS = Glasgow outcome scale. *Significant difference with D_0 within group, $P < 0.05$.

ROC curve analysis of the SVV also indicated that the best cut-off was SVV ≥ 13.5%, which verified our hypothesis that the common threshold of SVV > 13% was not appropriate for all situations with all patients. The positive standard for fluid therapy used in this study was ΔCI > 15% before and after treatment, a standard used in most clinical trials [16, 19]. The outcomes of SVV, IVC-CI, CI, CVP, MAP and HR were evaluated using the AUC analysis. SVV and IVC-CI had very good predictability with AUC > 0.7, which indicated that the Vigileo system and inferior vena cava ultrasonography can effectively guide fluid therapy, and the pre-diction was more accurate. Our results were also consistent with other clinical trials [1, 16]. However, traditional indicators, such as CI, CVP, MAP and HR, did not have as good a prediction as SVV and IVC-CI.

It has been widely reported that TNF-α, which elevates in the early stage of trauma, is positively correlated with the severity of trauma [20]. IL-6 is mainly released by immune cells, such as monocytes and T cells, and has a significant correlation with the inflammatory response [21]. IL-10 is an inflammatory inhibitor and can reflect a response to stress - higher IL-10 means a stronger anti-inflammatory ability [22]. Additionally, CRP and COR are also secreted under stress and cause the inflammatory response [23]. Funk found that patients with abdominal surgery had lower levels of TNF-α and CRP using the GDT therapy while undergoing an operation [24]. In our study, the results also showed that TNF-α was lower, and IL10 was significantly increased using the combined methods of GDT therapy. This could be interpreted as meaning that proper fluid administration can change the cytokine levels and reduce the traumatic and surgical stress responses, resulting in a reduction of the body's inflammation level.

Compared with other studies, Meng [25] used SVV to guard fluid therapy in patients with severe perioperative craniocerebral trauma, and this resulted in no significant difference in the fluid input between the two groups. Their results differed from ours, probably because we used an individualized fluid therapy threshold and reduced fluid input in the test group. Gu [26] studied different SVV thresholds in high-risk abdominal surgery, and the results showed that between 9% and 14%, the SVV could guard the fluid therapy, which was generally consistent with our results of SVV ≥ 13.5%. Huang [27] studied patients with sepsis ARDS, and found that patients in the cardiopulmonary ultrasound group had a lower ICU mechanical ventilation time.

There are some limitations in this study that should be mentioned. We did not explore the advantages and disadvantages of SVV and cardiopulmonary ultrasound in fluid management.

Table 5. ROC analysis for the prediction of fluid responsiveness

	AUC	95% CI	Threshold	Sensitivity (%)	Specificity (%)	*P* value
IVC-CI (%)	0.853	0.808-0.898	34.98	92.55	63.13	< 0.001
SVV (%)	0.831	0.784-0.877	13.5	92.55	72.35	< 0.001
CI (L/min.m^2)	0.666	0.592-0.739	2.95	32.98	97.24	< 0.001
CVP (cmH$_2$O)	0.611	0.545-0.678	10.5	57.45	61.29	0.002
MAP (mmHg)	0.578	0.514-0.641	96.5	80.85	39.17	0.029
HR (bpm)	0.511	0.446-0.575	104.5	87.23	27.65	0.764

IVC-CI = inferior vena cava collapsibility index; SVV = stroke volume variation; CI = cardiac index; CVP = central venous pressure; MAP = mean arterial pressure; HR = heart rate; bpm = beats per minute; 95% CI = 95% confidence interval.
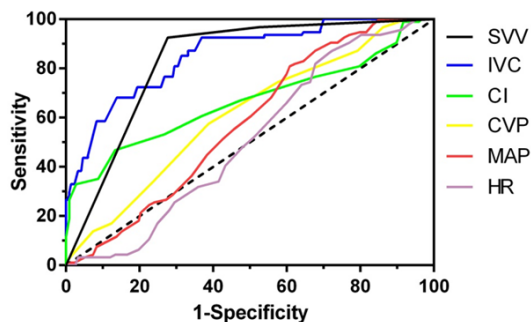

Figure 3. ROC curve analysis of the different endpoints for predicting fluid responsiveness in patients with ARDS caused by severe craniocerebral trauma. ROC = receiver operating characteristics; IVC-CI = inferior vena cava collapsibility index; SVV = stroke volume variation; CI = cardiac index; CVP = central venous pressure; MAP = mean arterial pressure; HR = heart rate.

Another limitation is that we did not take part in the clinical treatment in the ICU. We supposed that if more precise fluid therapy was used in ICU by SVV and cardiopulmonary ultrasound, more superiority would be detected. Additionally, the molecular mechanisms were not included in our research, but they should be discussed in the future.

In summary, the variable SVV threshold benefited guiding perioperative fluid therapy in patients with ARDS caused by severe craniocerebral trauma, and cardiopulmonary ultrasound can successfully evaluate priority. In combination with these two methods, less fluid was infused to the patients during their operations with higher PaO$_2$/FiO$_2$, and a shorter mechanical ventilation time required in the ICU.

Acknowledgements

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Li-Wei Wang, Department of Anesthesiology, Xuzhou Central Hospital, 199 South Jiefang Road, Xuzhou 221009, China. Tel: +86-516-83956181; E-mail: wangliwei_tougao@sohu.com

References

[1] Moretti R and Pizzi B. Inferior vena cava distensibility as a predictor of fluid responsiveness in patients with subarachnoid hemorrhage. Neurocrit Care 2010; 13: 3-9.

[2] Munoz-Bendix C, Beseoglu K and Kram R. Extracorporeal decarboxylation in patients with severe traumatic brain injury and ARDS enables effective control of intracranial pressure. Crit Care 2015; 19: 381.

[3] Kogan A, Segel MJ, Ram E, Raanani E, Peled-Potashnik Y, Levin S and Sternik L. Acute respiratory distress syndrome following cardiac surgery: comparison of the american-european consensus conference definition versus the berlin definition. Respiration 2019; 97: 518-524.

[4] Hussmann B, Schoeneberg C, Jungbluth P, Heuer M, Lefering R, Maek T, Hildebrand F, Lendemans S and Pape HC. Enhanced prehospital volume therapy does not lead to improved outcomes in severely injured patients with severe traumatic brain injury. BMC Emerg Med 2019; 19: 13.

[5] Rodling Wahlstrom M, Olivecrona M, Nystrom F, Koskinen LO and Naredi S. Fluid therapy and the use of albumin in the treatment of severe traumatic brain injury. Acta Anaesthesiol Scand 2009; 53: 18-25.

[6] Stein DM, Feather CB and Napolitano LM. Traumatic brain injury advances. Crit Care Clin 2017; 33: 1-13.

[7] Min JJ, Lee JH, Hong KY and Choi SJ. Utility of stroke volume variation measured using non-invasive bioreactance as a predictor of fluid responsiveness in the prone position. J Clin Monit Comput 2017; 31: 397-405.

[8] Willars C, Dada A, Hughes T and Green D. Functional haemodynamic monitoring: the value of SVV as measured by the LiDCORapid in predicting fluid responsiveness in high risk vascular surgical patients. Int J Surg 2012; 10: 148-152.

[9] Li J, Ji FH and Yang JP. Evaluation of stroke volume variation obtained by the FloTrac/Vigileo system to guide preoperative fluid therapy in patients undergoing brain surgery. J Int Med Res 2012; 40: 1175-1181.

[10] Yi L, Liu Z, Qiao L, Wan C and Mu D. Does stroke volume variation predict fluid responsiveness in children: a systematic review and meta-analysis. PLoS One 2017; 12: e0177590.

[11] Jeong DM, Ahn HJ, Park HW, Yang M, Kim JA and Park J. Stroke volume variation and pulse pressure variation are not useful for predicting fluid responsiveness in thoracic surgery. Anesth Analg 2017; 125: 1158-1165.

[12] Gui J, Yang Z, Ou B, Xu A, Yang F, Chen Q, Jiang L and Tang W. Is the collapsibility index of the inferior vena cava an accurate predictor for the early detection of intravascular volume change? Shock 2018; 49: 29-32.

[13] Preau S, Bortolotti P, Colling D, Dewavrin F, Colas V, Voisin B, Onimus T, Drumez E, Durocher A, Redheuil A and Saulnier F. Diagnostic accuracy of the inferior vena cava collapsibility to predict fluid responsiveness in spontaneously breathing patients with sepsis and acute circulatory failure. Crit Care Med 2017; 45: e290-e297.

[14] Zhang J and Critchley LA. Inferior vena cava ultrasonography before general anesthesia can predict hypotension after induction. Anesthesiology 2016; 124: 580-589.

[15] Messina A, Pelaia C, Bruni A, Garofalo E, Bonicolini E, Longhini F, Dellara E, Saderi L, Romagnoli S, Sotgiu G, Cecconi M and Navalesi P. Fluid challenge during anesthesia: a systematic review and meta-analysis. Anesth Analg 2018; 127: 1353-1364.

[16] Lu N, Xi X, Jiang L, Yang D and Yin K. Exploring the best predictors of fluid responsiveness in patients with septic shock. Am J Emerg Med 2017; 35: 1258-1261.

[17] Jennett B and Bond M. Assessment of outcome after severe brain damage. Lancet 1975; 1: 480-484.

[18] Hoiseth LO, Hoff IE, Hagen OA, Landsverk SA and Kirkeboen KA. Agreement between stroke volume measured by oesophageal Doppler and uncalibrated pulse contour analysis during fluid loads in severe aortic stenosis. J Clin Monit Comput 2015; 29: 435-441.

[19] Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR and Teboul JL. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 2000; 162: 134-138.

[20] Wu H, Wang G, Li S, Zhang M, Li H and Wang K. TNF-alpha-mediated-p38-dependent signaling pathway contributes to myocyte apoptosis in rats subjected to surgical trauma. Cell Physiol Biochem 2015; 35: 1454-1466.

[21] Mommsen P, Barkhausen T, Zeckey C, Andruszkow H, Krettek C and Neunaber C. Effects of trauma-hemorrhage and IL-6 deficiency on splenic immune function in a murine trauma model. Mediators Inflamm 2012; 2012: 186709.

[22] Andreas L. Systemic inflammation after trauma. Injury 2007; 12.

[23] Zhong W, Zhang Z, Zhao P, Shen J, Li X, Wang D, Li G and Su W. The impact of initial systemic inflammatory response after aneurysmal subarachnoid hemorrhage. Turk Neurosurg 2017; 27: 346-352.

[24] Funk DJ, HayGlass KT, Koulack J, Harding G, Boyd A and Brinkman R. A randomized controlled trial on the effects of goal-directed therapy on the inflammatory response open abdominal aortic aneurysm repair. Crit Care 2015; 19: 247.

[25] Meng Lijiang, Xiong Fuli and Shan Z. The effect of stroke volume variability on the volumetric treatment of patients with severe craniocerebral injury surgery. Chinese Journal of Anesthesiology 2018; 38: 1119-1123.

[26] Gu Jie, Gao Zhifeng and Xiaoyu W. Effects of target-directed fluid therapy based on different targets on perioperative vascular endothelial polysaccharide coating in patients with high-risk abdominal surgery: a prospective randomized controlled trial. Chinese Journal of Anesthesiology 2018; 38: 707-711.

[27] Huang D, Ma H, Xiao Z, Blaivas M, Chen Y, Wen J, Guo W, Liang J, Liao X, Wang Z, Li H, Li J, Chao Y, Wang XT, Wu Y, Qin T, Su K, Wang S and Tan N. Diagnostic value of cardiopulmonary ultrasound in elderly patients with acute respiratory distress syndrome. BMC Pulm Med 2018; 18: 136.