

# Goal-directed fluid optimization based on stroke volume variation and cardiac index during one-lung ventilation in patients undergoing thoracoscopy lobectomy operations: a pilot study

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**OBJECTIVES:** This pilot study was designed to utilize stroke volume variation and cardiac index to ensure fluid optimization during one-lung ventilation in patients undergoing thoracoscopic lobectomies.

**METHODS:** Eighty patients undergoing thoracoscopic lobectomy were randomized into either a goal-directed therapy group or a control group. In the goal-directed therapy group, the stroke volume variation was controlled at  $10\% \pm 1\%$ , and the cardiac index was controlled at a minimum of  $2.5 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ . In the control group, the MAP was maintained at between 65 mm Hg and 90 mm Hg, heart rate was maintained at between 60 BPM and 100 BPM, and urinary output was greater than  $0.5 \text{ mL/kg}^{-1}/\text{h}^{-1}$ . The hemodynamic variables, arterial blood gas analyses, total administered fluid volume and side effects were recorded.

**RESULTS:** The  $\text{PaO}_2/\text{FiO}_2$ -ratio before the end of one-lung ventilation in the goal-directed therapy group was significantly higher than that of the control group, but there were no differences between the goal-directed therapy group and the control group for the  $\text{PaO}_2/\text{FiO}_2$ -ratio or other arterial blood gas analysis indices prior to anesthesia. The extubation time was significantly earlier in the goal-directed therapy group, but there was no difference in the length of hospital stay. Patients in the control group had greater urine volumes, and they were given greater colloid and overall fluid volumes. Nausea and vomiting were significantly reduced in the goal-directed therapy group.

**CONCLUSION:** The results of this study demonstrated that an optimization protocol, based on stroke volume variation and cardiac index obtained with a FloTrac/Vigileo device, increased the  $\text{PaO}_2/\text{FiO}_2$ -ratio and reduced the overall fluid volume, intubation time and postoperative complications (nausea and vomiting) in thoracic surgery patients requiring one-lung ventilation.

**KEYWORDS:** Stroke Volume; Cardiac Output; Fluid Therapy; One-Lung Ventilation.

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## INTRODUCTION

Perioperative goal-directed fluid therapy (GDT) is a cornerstone of tissue perfusion and oxygenation, and it can improve surgical outcomes. Optimal perioperative fluid management is essential for reducing postoperative complications and mortality (1,2) rates. Surgical patients are more likely to have serious complications and die if they have limited physiologic reserves. Proper fluid administration can

reduce the stress response to surgical trauma and, thus, support recovery, particularly in cardiothoracic surgery (3-5).

Fluid management in thoracic surgery is of particular importance because of the influence of one-lung ventilation (OLV). It has been reported that OLV can be a cause of postoperative pulmonary edema (6,7). Edema formation after OLV has been attributed to oxidative stress during and immediately following OLV during reexpansion of the deflated lung after conventional ventilation has been reestablished (8,9). Therefore, OLV might act as an additional factor in aggravating perioperative pulmonary fluid overload. Lung lobectomy also leads to an increase in pulmonary proinflammatory cytokines and local edema.

A new stroke volume variation (SVV) and cardiac output monitoring device, the Vigileo-FloTrac system (Edwards Lifescience, Irvine, CA, USA), is based on arterial pulse contour and does not require external calibration, thermodilution or

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dye dilution; therefore, it offers the possibility of almost beat-to-beat measurements of cardiac output and SVV. The accuracy of this device in assessing SVV and cardiac output has been tested in numerous settings with varying results (10-19). Moreover, the past limitations of SVV use, such as open chest, OLV and arrhythmia, have been relaxed as the result of further investigations (20-22).

In recent years, GDT, based on SVV derived from the FloTrac system, has been used in many types of surgery to improve postoperative outcomes (23-25). However, SVV should be interpreted with caution. Under stable mechanical ventilation, SVV is a marker of position on the Frank-Starling curve and not an indicator of blood volume status or of cardiac preload. The slope of the Frank-Starling curve differs among patients depending on cardiac contractility: the slope decreases in patients with decreased cardiac contractility and increases in those with increased cardiac contractility. Therefore, minimizing SVV by volume loading can cause overhydration in patients with increased cardiac contractility and occult hypovolemia in those with decreased cardiac contractility (26). GDT based on SVV can improve postoperative outcomes when the other hemodynamic parameters, such as cardiac output and mean arterial pressure, are also considered. We agree with other authors' findings that GDT based simply on stroke volume optimization does not confer any additional benefits over conventional liberal fluid therapy. However, GDT based on a multiparametric approach could improve postoperative outcomes because every hemodynamic variable has limitations and interferes with other variables (27). This pilot study was designed to utilize the SVV and cardiac indices ([CIs], cardiac output/body surface area) to ensure fluid optimization during one-lung ventilation in patients undergoing thoracoscopic lobectomy.

## ■ MATERIALS AND METHODS

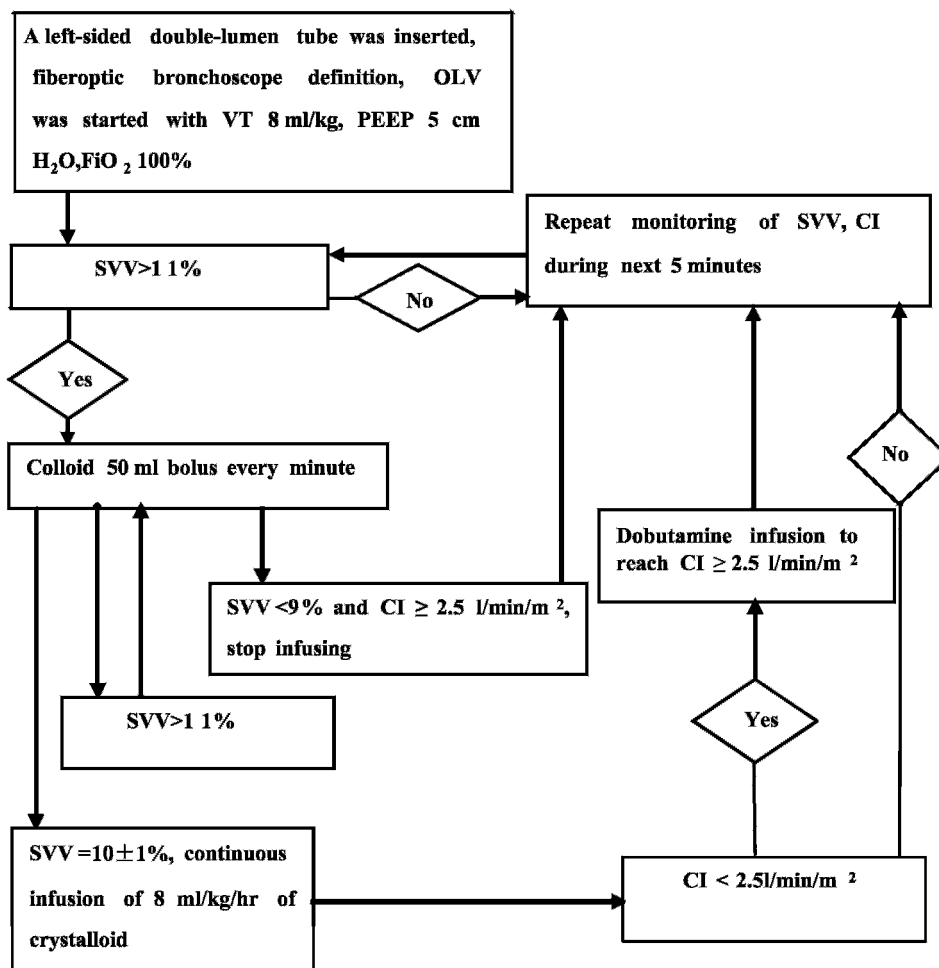
We obtained institutional ethics committee approval from the First Affiliated Hospital College of Medicine (Zhejiang University) and written informed consent from the study participants. Eighty patients satisfied the following inclusion criteria and were enrolled in our study: age 18–60 years old; American Society of Anesthesiologists physical status I–II; and sinus rhythm. The exclusion criteria included risk of hepatic/renal/cardiac dysfunction, severe obesity (body mass index >35), severe aortic regurgitation, frequent ventricular extrasystoles and one-lung ventilation time less than 1 hour. All of the patients underwent thoracoscopic lobectomy during one-lung ventilation. This prospective, randomized trial was performed in a university-affiliated hospital. The 80 patients were randomized preoperatively, using a closed envelope system, into either the GDT group or the control group. In the GDT group, SVV was controlled at  $10\% \pm 1\%$ , and CI was controlled at minimum of  $2.5 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ . In the control group, the mean arterial pressure was maintained at between 65 mm Hg and 90 mm Hg, heart rate was maintained at between 60 BPM and 100 BPM, and urinary output was greater than  $0.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . The monitoring included invasive arterial pressure, electrocardiography, percutaneous oxygen saturation and end-tidal carbon dioxide. Before anesthesia induction, a 20 G arterial line was inserted into the radial artery of the non-dominant forearm, and baseline measurements and blood were obtained for the laboratory tests. The optimal

pressure signal damping was assessed using a flush test before the first measurements. SVV, CI, cardiac output, stroke volume and stroke volume index were measured by using the Vigileo-FloTrac system. General anesthesia was induced with  $0.7 \mu\text{g}/\text{kg}$  sufentanil,  $2.5 \text{ mg}/\text{kg}$  propofol and  $0.15 \text{ mg}/\text{kg}$  vecuronium. After anesthesia induction, a left-sided double-lumen tube (Broncho-cath, Tyco Healthcare, Argyle, Mansfield, MA, USA) was inserted, and each patient was adjusted using a fiberoptic bronchoscope. Anesthesia was maintained with 1.0–1.5% sevoflurane, and the depth of anesthesia was maintained at 35–50 using a bispectral index monitor (v. 4.0; Aspect Medical System, Natick, MA, USA). The intraoperative inspired  $\text{O}_2$  concentration ( $\text{FiO}_2$ ) was 100%. Additional sufentanil and vecuronium were administered as needed for further relaxation. OLV was started with a ventilatory volume of  $8 \text{ mL}/\text{kg}$  and positive end-expiratory pressure of  $5 \text{ cm H}_2\text{O}$ , and either the ventilation rate was 12 breaths/minute or it was adjusted to maintain an arterial partial pressure of carbon dioxide between 36 mm Hg and 44 mm Hg. The inspiratory-expiratory ratio was 1:2. The details of the modified hemodynamic monitoring protocols for the GDT group are summarized in Figure 1. Intraoperative basal fluid replacement was realized in both groups with continuous infusion of  $8 \text{ mL}/\text{kg}/\text{hr}$  of crystalloid solution. When the SVV was greater than 11%, volume optimization was achieved by administering a 50 mL bolus of colloid solution (Voluven 130/0.4 6%; Fresenius Kabi AG, Bad Homburg, Germany) every minute until a stable SVV value of  $\leq 9\%$  was reached for 2 minutes. The total administered crystalloid and colloid volume were recorded for each patient. When the mean arterial pressure dropped below 60 mm Hg despite fluid resuscitation or during sudden blood loss, continuous phenylephrine administration of  $2 \mu\text{g}/\text{min}$  was initiated. An infusion of dobutamine  $2\text{--}5 \mu\text{g}/\text{min}/\text{kg}$  was started to maintain the CI between  $2.5 \text{ L}/\text{min}/\text{m}^2$  and  $4 \text{ L}/\text{min}/\text{m}^2$  under low cardiac output state conditions (CI less than  $2.5 \text{ L}/\text{min}/\text{m}^2$ ). Ephedrine boluses of 5–15 mg were allowed in addition to colloid infusion to treat a systolic arterial pressure below 90 mm Hg or a mean arterial pressure less than 65 mm Hg (e.g., during clamp release, sudden large blood loss, etc.). The goal was to maintain the mean arterial pressure above 70 mm Hg. These episodes were recorded as hypotensive events and were submitted to analysis. After extubation, SVV-guided fluid management was discontinued because SVV is not validated for use during spontaneous breathing. In the control group, the anesthesiologist was free to administer additional fluids (both crystalloids and colloids) or to use vasoactive substances to maintain the blood pressure, diuresis and heart rate within normal ranges (mean arterial pressure  $>65 \text{ mm Hg}$ , heart rate 60–100 BPM, urine output  $>0.5 \text{ mL}/\text{kg}/\text{h}$ ). In both groups, baseline hemodynamic measurements and arterial blood gas analyses were performed before inducing anesthesia ( $T_1$ ) and 10 minutes before the termination of OLV ( $T_2$ ).

Side effects (nausea and vomiting) were recorded in both groups for 24 h after the end of surgery. Blood loss was mitigated with fluids and a hemoglobin value less than  $8 \text{ mg}/\text{dL}^{-1}$  was considered to be a trigger for the transfusion of packed red blood cells.

## Statistical analysis

Patient data were collected and are presented as the means  $\pm$  standard deviations, medians (interquartile ranges) and



**Figure 1** - Fluid management protocol based on SVV and CI (CI, cardiac index; SVV, stroke volume variation; PEEP, positive end-expiratory pressure; VT, tidal volume; FiO<sub>2</sub>, fraction of inspired oxygen).

direct counts, as appropriate. For a test of normal distribution, the Kolmogorov-Smirnov test was applied. Continuous data with normal distribution were tested with paired or unpaired t-tests. Non-normally distributed data were subjected to the Mann-Whitney U-test and Wilcoxon’s rank-sum test for unpaired and paired results, respectively. Changes in the time-dependent variables were measured using analysis of variance on repeated measurements or Friedman’s test. Categorical data were tested using the chi-square test and the chi-square test for trends. The data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 15.0) for Windows™, and  $p < 0.05$  was considered statistically significant.

**Ethics**

Study approval was obtained from the Ethics Committee of Zhejiang University (China).

**RESULTS**

The patients’ characteristic data were similar between the two groups (Table 1). Furthermore, no derangements in metabolic parameters were found in either group. The PaO<sub>2</sub>/FiO<sub>2</sub>-ratio before the end of OLV in the GDT group was significantly higher than that in the control group, but

there was no difference between the GDT group and the control group for the PaO<sub>2</sub>/FiO<sub>2</sub>-ratio or other arterial blood gas analysis indices prior to anesthesia (Table 2). The extubation time was significantly earlier in the GDT group, but there was no difference in the length of hospital stay. The patients in the control group had greater urine volumes

**Table 1** - Demographic characteristics and laboratory examinations.

	Control group (n = 30)	GDT group (n = 30)
Age (yr)	61.0 ± 8.7	59.9 ± 8.9
Sex (F/M)	14/16	12/18
Height (cm)	162 ± 5	162 ± 5
Weight (kg)	67 ± 9.7	71 ± 10.3
Heart rate (beats/min)	74 ± 3	76 ± 4
Systolic pressure	109.0 ± 28	106.6 ± 24
Diastolic pressure	62.0 ± 14.8	59.9 ± 11.4
MAP (mm Hg)	79.1 ± 19.2	74.8 ± 17.6
GPT (IU/L)	25.83 ± 8.15	23.31 ± 6.53
GOT (U/L)	21.82 ± 7.92	22.15 ± 9.26
Creatinine	63 ± 11	80 ± 15
Predicted FEV <sub>1</sub> %	86.5 ± 11.4	83.96 ± 8.7

The data are the means ± standard deviation. GPT: glutamic-pyruvic transaminase. GOT: aspartate amino-transferase. FEV1: Forced expiratory volume in one second.



**Table 2 - Arterial blood gas analysis.**

	Control group (n = 30)		GDT group (n = 30)	
	T1	T2	T1	T2
PH	7.44 (0.03)	7.33 (0.11)	7.40 (0.03)	7.43 (0.02)
PO <sub>2</sub>	81 (9)	241.9 (60.1)	86.0 (10)	334.5 (87.3)*
PaO <sub>2</sub> /FiO <sub>2</sub>	385.7 (44.2)	241.9 (60.1)	409.5 (51.7)	334.5 (87.3)*
PCO <sub>2</sub>	38.5 (3.9)	41.88 (6.1)	37.8 (3.2)	41.2 (4.6)
HCO <sub>3</sub>	25.8 (1.67)	27.34 (1.53)	26.0 (1.73)	26.9 (1.84)
Hb	13.26 (1.05)	11.74 (1.11)	12.89 (1.26)	13.01 (1.32)
Lac	1.77 ± 0.8	1.79 ± 0.62	1.86 ± 0.66	1.82 ± 0.61
K	3.9 (0.5)	4.0 (0.4)	3.8 (0.5)	4.2 (1.2)
Na	136.3 (5.2)	139.9 (2.2)	137.1 (5.1)	135.4 (7.3)
Glu	5.32 (0.91)	5.63 (0.52)	5.81 (1.69)	6.09 (2.01)

The data are the totals (percentages) or means ± standard deviation. \*p<0.05 compared with 0.05% within groups. T1: before induction, air inhaled. T2: at the end of one-lung ventilation. Fraction of inspired oxygen: 100%.

and were given greater colloid and overall fluid volumes. Nausea and vomiting were significantly reduced in the GDT group (Table 3). Dobutamine was used in 5 patients from the GDT group when the CI was <2.5 l/min/m<sup>2</sup>; therefore, the ephedrine usage time in the GDT group was less than that in the control group.

**DISCUSSION**

To our knowledge, this is the first study using the Vigileo-FloTrac monitor in the perioperative setting to guide fluid management, with CI and SVV limited to small ranges instead of using only the top limit value.

The present study showed that in patients undergoing OLV, the PaO<sub>2</sub>/FiO<sub>2</sub>-ratio before the end of OLV in the GDT group was significantly higher than that in the control group. Extubation time was significantly earlier than in the

**Table 3 - Perioperative period data.**

	Control group (n = 30)	GDT group (n = 30)
Duration of anesthesia (min)	117 ± 44	123 ± 48
Extubation time (min)	25 ± 12	6 ± 3*
Urinary output (ml·kg <sup>-1</sup> ·h <sup>-1</sup> )	2.2 ± 1.1	0.7 ± 0.3*
Blood loss (ml)	20 ± 5	218
Crystalloids (ml)	715 ± 120	625 ± 100
Colloids (ml)	670 ± 105	360 ± 85*
Total volume infused	1,385 ± 350	985 ± 135*
MAP (mm Hg)	80.6 ± 16.1	74.5 ± 18.3
Heart rate (bpm)	69 ± 15	75 ± 18
Dobutamine (case)	0	5*
Ephedrine (case)	9	3*
Length of hospital stay	5	4.5
Complications until hospital discharge		
Re-intubation	0	0
Nausea and vomiting	12	6*
No defecation >2 days	0	0
Acute renal failure	0	0
Bronchial fistula	0	0
Re-operation for bleeding	0	0
Atelectasis	0	0
Pulmonary infection	4	3

The data are the totals (percentage) or means ± SD. \*p<0.05 compared with 0.05% within groups.

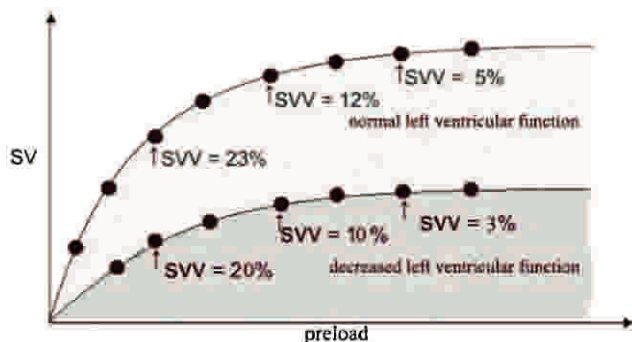
The means of the values were taken automatically every 5 minutes.

GDT group, which also had a reduced intubation time. The control group patients had greater urine volumes and were administered greater colloid and overall fluid volumes. That is, fluid management guided by SVV and CI could reduce pulmonary fluid overload and improve pulmonary oxygen exchange, rather than destabilize the hemodynamics. The combination of SVV and CI can be practically applied in patients undergoing OLV, but the disturbing data on arrhythmias, posture changes and artery sensor occlusion should be excluded.

Our results were somewhat similar to those of Haas et al. (24), who showed that SVV-guided fluid management during lateral thoracotomy and OLV did not result in pulmonary fluid overload. Although oxygenation was reduced, pulmonary function remained within a clinically acceptable range. Our experimental design was different from that of the Haas et al. study in that their study was not designed to demonstrate the clinical advantage of SVV-guided fluid management compared to a control group. Several indices, including fluid administration, were compared between lung surgery and esophagectomy surgery patients. Therefore, the results of Haas et al. must be interpreted with caution. In addition, although they monitored SVV, pulse index and continuous cardiac output, Haas et al. did not combine SVV with other cardiac function monitoring indices, such as cardiac index and cardiac output.

In conventional clinical settings, hemodynamic variables, such as heart rate, mean arterial pressure and central venous pressure, are controlled by fluid therapy, blood transfusions and vasopressor administration. However, intraoperative hypovolemia is common and can be a potent cause of organ dysfunction and increased postoperative morbidity and mortality. Therefore, dynamic parameters, such as arterial pulse pressure variation and SVV, have been identified as the best indicators in mechanically ventilated patients. Pulse pressure variation and SVV should be interpreted with caution; however, under stable mechanical ventilation, pulse pressure variation and SVV are only markers of the position on the Frank-Starling curve and are not indicators of blood volume status or markers of cardiac preload. When not considering cardiac output maximization as a target, fluid responsiveness does not indicate whether fluids are needed. Patients should not receive fluids only because of a high SVV value. A clinical approach is needed to diagnose those patients presenting with circulatory failure who would benefit from increasing stroke volume. Most of these studies have used colloid titration to increase cardiac output by bringing patients to the plateau of the Frank-Starling curve (achieved when cardiac output no longer increases after fluid challenge). Such cardiac output maximization can be attained using cardiac output monitoring or SVV or its surrogates (cardiac output maximization is achieved by minimizing SVV or its surrogates).

Regarding normal hemodynamics, the GDT group was able to control the preload accurately. After the CI decreased with the arterial blood pressure decline, we first treated with dobutamine and then using the SVV target value as a fluid infusion guide. Because the CI decrease caused a cardiac function curve slope reduction, the mean SVV values increased, but the patients were unsuitable for fluid replacement (Figure 2), which is a key treatment for improving cardiac function and avoiding fluid overload. In



**Figure 2** - SVV and Frank-Starling curve. The relationship between preload and SV in different left ventricular functions. Individual cardiac function could cause different cardiac reactions to a fluid bolus.

our study, when the CI value was in the normal range, the SVV value guided fluid infusion. If the CI value was less than the normal range, we first corrected the CI values to normal. We speculated that fluid management guided by SVV and CI would reduce the overall fluid infusion perioperatively. Our results were consistent with this hypothesis. The volume of colloids and total volume infused were lower in the GDT group than in the control group.

Each patient has an individual Frank-Starling curve; therefore, in different types of operations or patient situations, the corresponding cutoff values are different. The optimal cut-off value for SVV is still uncertain in different clinical scenarios. A study of living donor right hepatectomy patients proposed that the optimal cutoff value for SVV predicting blood loss of 700 mL was 6% (15). In septic shock patients, the optimal threshold value for distinguishing between responders and nonresponders was 10% for SVV (28). Wu et al. found that a 14% supine SVV predicted a decline in CI (20). These inconclusive results show that further evaluation of dynamic variables is needed, and the results of protocols based on SVV only should be viewed cautiously. We used the  $10\% \pm 1\%$  threshold scope proposed by Suehiro (12), which was the best available recommended value for the Vigileo-FloTrac at the time that our protocol was prepared. A sustained change in SVV greater than 11% or less than 9% for a period of 3 minutes was required to start an intervention, to exclude possible bias because of surgical manipulations or other influences.

In this study, an interesting phenomenon occurred. In the experimental group, it was difficult to maintain the SVV at 15%. After lateral positioning and OLV, the SVV value was nearly 15%; therefore, a small amount of fluid caused the SVV value to drop to less than 15%. Moreover, after the SVV value was less than 15%, it was difficult to raise it. The cause of this phenomenon was unclear.

Although most investigations have shown that goal-directed fluid therapy can effectively improve patient outcomes, it remains undetermined whether greater fluid infusion guided by GDT is helpful. Lopes et al. (4) demonstrated that the GDT group received more fluid than the control group. The control group received fluid intraoperatively at the discretion of the anesthetist, according to the protocol proposed by Kobayashi et al. (4). Further studies by Benes et al. (22) and Mayer et al. (23) both showed that the SVV-guided group received significantly

larger volumes of colloid infusions, but the volumes of infused crystalloids and the amounts of blood products and blood loss did not differ between the groups.

However, a case series of laparoscopic adrenalectomies in patients with pheochromocytoma demonstrated that both total infusion volume and urine output were significantly higher in the control group compared to the SVV-guided group (29). Total blood loss was similar between the two groups. The values of the net fluid balance divided by body weight and of the total anesthesia period were significantly lower in the SVV-guided group compared with the control group. These data suggest that SVV monitoring is helpful for estimating the optimal volume for fluid supplementation, and it could prevent excessive fluid infusion during surgical procedures. The difference between these findings might have resulted from two causes: first, the control group received fluids at the discretion of the anesthetist, resulting in significant variation; second, Isosu et al. omitted target SVV values less than 10% and treated SVV values between 1% and 10% identically, thereby causing an obvious distinction in the amount of fluid infusion. In our study, we paid attention to these differences and improved the clinical protocol; therefore, the total amount of fluid infusion in the SVV-guided group was lower than that in the control group.

There were some possible limitations of this study worth noting. First, we should have designed another group in which we did not use SVV+CI, but only SVV, to guide fluid management. Second, we ignored the timing of the fluid administration, but Noblett et al. (30) indicated that the timing of fluid administration might be more critical than the volume of fluid administered. Third, our patients underwent thoracoscopic lobectomy operations with OLV; therefore, our results might not be applicable to other patient groups undergoing other procedures. Fourth, different types of lobectomy should be studied because of their correlations to extubation times.

In conclusion, the results of this study demonstrated that an optimization protocol, based on stroke volume variation and cardiac index obtained with the FloTrac/Vigileo device, increased the  $\text{PaO}_2/\text{FiO}_2$ -ratio and reduced the overall fluid volume, intubation time and nausea and vomiting in thoracic surgery patients requiring one-lung ventilation.

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## AUTHOR CONTRIBUTIONS

Zhang J designed the study, conducted the research, and wrote the manuscript. Chen CQ and Lei XZ helped to design the study, conducted the research, and wrote the manuscript. Feng ZY helped to design the study and conducted the research. Zhu SM is the corresponding author, designed the study and revised the manuscript. All of the authors read and approved the final manuscript.

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