Original Article

Goal-directed fluid restriction using stroke volume variation and cardiac index during one-lung ventilation: a randomized controlled trial

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Background: Goal-directed therapy confers a strong prognosis in patients undergoing major cardiac or noncardiac surgery. The present study investigated whether intraoperative goal-directed fluid restriction (GDFR) using stroke volume variation (SVV) and cardiac index could improve oxygenation and postoperative outcome in patients undergoing one-lung ventilation (OLV).

Methods: A Total of 168 patients scheduled for elective thoracoscopic lobectomy under OLV were randomized into the GDFR protocol (group G) or conventional fluid therapy groups (group C). Patients in group C underwent conventional fluid therapy based on mean arterial pressure (MAP), central venous pressure (CVP), and urine volume, whereas those in group G received GDFR protocol associated with the SVV from 10–13% and the cardiac index was controlled at a minimum of 2.5 L/min/m^2. The primary outcome variable was PaO_2/FiO_2. The secondary outcomes were other pulmonary variables and lung mechanics, inflammatory response, the incidence of postoperative pulmonary complications, and the length of hospital stay.

Results: During surgery, the PaO_2/FiO_2 ratio in group G was more than that of group C at 30 and 60 min after OLV, 10 min after re-expansion, and the end of the operation (259±29 *vs.* 314±34; 253±30 *vs.* 308±35; 341±34 *vs.* 394±39; 349±35 *vs.* 401±39, respectively, all P<0.001). Compared to conventional fluid therapy, GDFR protocol also significantly improved the hemodynamic and lung mechanics with the initiation of OLV. The incidence of postoperative pulmonary complications such as acute lung injury and pneumonia, and the length of hospital stay were decreased by GDFR protocol as compared to conventional fluid therapy (all P<0.05). However, there were no significant differences between groups with respect to the concentration of serum tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10).

Conclusions: The GDFR protocol based on SVV and cardiac index applied in patients undergoing OLV improves intraoperative pulmonary oxygenation. It can also reduce the postoperative complications and length of hospital stay. However, the GDFR strategy cannot reduce the local or systemic inflammation.

Trial registration: Chinese Clinical Trials Register ChiCTR-INR-16008288, Registered 20 April, 2016.

Keywords: Fluid therapy; stroke volume variation (SVV); one-lung ventilation (OLV); lung function

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Introduction

Fluid management is an important issue for patients during surgery. The intraoperative fluid infusion balance between hypovolemia and overload has been identified as a major contributing factor to avoid the postoperative complications, such as systemic inflammatory response syndrome, ileus, increased cardiac demands, and even multiple organ failure (1-3). The conventional fluid management is based on the clinical signs such as mean arterial pressure (MAP), central venous pressure (CVP), or urine output that are only slightly related to the hemodynamic goals of fluid administration (1). Previous studies indicated that fluid titration based on the measurements of functional hemodynamic variables, such as stroke volume variation (SVV), which was obtained by pulse contour analysis and variation of stroke volume during the respiratory cycle, was useful to exert a superior effect in improving end-organ perfusion and oxygenation. Similarly, it can also decrease the rate of postoperative complications in different surgical patients (4-8).

One-lung ventilation (OLV), a non-physiological ventilation approach, is widely used in thoracic surgery. Previous studies revealed that the incidence of postoperative acute lung injury (ALI) is 2–5% after major thoracic surgery (9). Although the exact pathogenesis of OLV-related ALI undergoing lobectomy has not been fully elucidated, previous studies have indicated that the intraoperative oxygenation dysfunction and overload fluid management during thoracic surgery has been identified as risk factors for lung injuries and other pulmonary complications such as pulmonary edema (10-13). For specific surgical procedures, reducing the amount of intraoperative fluid infusion and improving oxygenation is of paramount importance in thoracic surgery. Nevertheless, it is well known that the blinded or uncontrolled fluid restriction may cause other hypovolemia-related complications, such as tissue hypoxia, which play a potent role in organ dysfunction and increased postoperative morbidity and mortality (14,15).

Previous studies have demonstrated that SVV is useful to predict fluid responsiveness legitimately during OLV with acceptable levels of sensitivity and specificity (16,17). However, studies exploring the effect of intraoperative fluid restriction protocol based on advanced hemodynamic parameters on patients' oxygenation and postoperative prognosis during OLV are yet lacking. In the present study, we hypothesized that the use of cardiovascular measurements might be valuable in striking a balance between the risks of insufficient and excessive fluid intake. Therefore, we designed an intraoperative goal-directed fluid restriction (GDFR) protocol where minimal fluid maintenance according to the recent literature in patients during thoracic surgery (18).

The aim of the clinical study was to investigate the effect of intraoperative GDFR protocol using SVV and cardiac index on intrapulmonary oxygenation and postoperative outcomes in patients undergoing OLV. The primary outcome variable was PaO_2/F_iO_2, a useful variable for detecting impaired intrapulmonary oxygenation and gas exchange (19,20). The secondary outcomes were other pulmonary variables and pneumodynamics, inflammatory response, and the incidence of postoperative pulmonary complications.

Methods

Patients

Between April 2016 and February 2017, 180 adult patients diagnosed with primary non-small-cell lung cancer with a preoperative clinical stage IA or IB as assessed by computer tomography or positron emission tomography-computed tomography scan were scheduled for thoracoscopic lobectomy undergoing OLV, and those that satisfied the following inclusion criteria were recruited: aged between 18 and 60 years; American Society of Anesthesiologists physical (ASA) status I-II category; body mass index between 18.5 and 25kg/m^2. The exclusion criteria included severe impairment of renal and cardiac function (New York Heart Association classes III-IV); Preoperative abnormal lung function (forced expiratory volume in 1 s <50% of the predicted values); systemic or local active infections (clinically defined, leukocytosis, or the body temperature >38 ℃); Preoperative acid-base or electrolyte imbalance; Intraoperative frequent cardiac arrhythmias and OLV time <60 min.

Randomization and masking

All the enrolled patients were allocated in a 1:1 ratio to undergo fluid management during OLV into either the GDFR protocol group (group G) or the conventional fluid management group (group C). The randomization was stratified by sequential blocking based on the computer random number generator. Allocations details were kept in sealed envelopes marked by serial number. Before the induction of anesthesia, the sealed, numbered and opaque envelopes containing the treatment assignments were

opened by an independent anesthesiologist. The data assessment or analysis was performed by an independent research staff supervised by an independent statistician. To make sure the reliability of data acquisition, the patients, the clinical researchers for the collection of data and blood samples and postoperative follow-up team were all blinded to group allocation. Group allocation was scarcely revealed when the final data analysis was completed.

Anesthesia and monitoring

The patients received a restricted diet before surgery. Before the induction of anesthesia, the standardized central venous puncture was performed, and a 20-G arterial line (B. Braun Medical Inc., Bethlehem, PA, USA) was inserted into the radial artery of the nondominant forearm. The heart rate (HR), MAP, CVP, pulse oxygen saturation (SpO_2), end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$), temperature, and bispectral index (BIS) were continuously monitored on a multifunction screen (Philips Medizin, Hamburg, Germany). The SVV, cardiac index (CI), cardiac output, and stroke volume were measured by the FloTrac/Vigileo system (Edwards Lifesciences, Irvine, CA, USA).

General anesthesia was initiated with intravenous 0.05 mg/kg midazolam, 2 mg/kg propofol, 0.4 mg/kg sufentanil, and 1.0 mg/kg rocuronium. Subsequently, the intraoperative anesthesia was maintained with a continuous infusion of propofol (4–8 mg/kg/h) and remifentanil (0.05–0.2 μg/kg/min) in order to achieve a target BIS value between 40 and 50. After the induction of anesthesia, a left-sided double-lumen endobronchial tube (Mallinckrodt, Dublin, Ireland) was inserted and confirmed by bronchoscopy. Patients were ventilated in volume controlled mode by using an anesthesia machine (S/5 Avance, Datex-Ohmeda, Madison, USA) following the protocol with tidal volume (V_T) 8 mL/kg (two-lung ventilation) or 6 mL/kg (OLV), fraction of inspired oxygen (F_iO_2) 100%, inspiratory to expiratory time (I/E) ratio 1:2, and positive end-expiratory pressure (PEEP) 5 cmH_2O; the respiratory rates were adjusted to maintain the $P_{ET}CO_2$ between 35 and 45 mmHg. The continuous positive airway pressure (CPAP) of 1–2 cmH_2O to the nonventilated lung or recruitment maneuver to the ventilated lung was applied for a limited period to the non-dependent lung when the peripheral saturation decreased below 90%. The nasopharyngeal temperature was maintained >36 ℃ by fluid warming devices or medical warming blankets. The intermittent additional sufentanil or cisatracurium was administered during surgery as per the requirement.

Intervention protocol

All the practitioners in this study were experienced with the FloTrac/Vigileo device. In both groups, the intraoperative basal fluid replacement was achieved by continuous infusion of the 4 mL/kg/h crystalloid solution after general anesthesia induction. For group C, the anesthesiologist administered additional fluids in those who underwent conventional fluid management according to the principles of Miller's Anesthesia or used vasoactive substances, if necessary, aiming at MAP >65 mmHg, HR 60–100 bpm, CVP 6–12 mmHg, and the urine output >0.5 mL/kg/h. Patients in group G received the intraoperative fluid management during OLV, and the protocol was summarized in *Figure 1*. In the case that SVV was >13%, 4 mL/kg bolus of colloid (hydroxyethyl starches 130/0.4 in 6%, Fresenius Kabi AG, Bad Homburg, Germany) infused over 5 min was administered, and if the SV increased by more than 10%, the bolus was repeated until SVV <13%. In the case that SVV was <10%, then the bolus was suspended or infused with a slow speed in order to maintain SVV >10%. An infusion of dobutamine 3–5 μg/kg/min was administered after the SV failed to increase by more than 10% or CI less than 2.5 L/min/m^2. The intravenous norepinephrine bolus of 20 μg was allowed when the fluid infusion failed to maintain the MAP >65 mmHg. The hemodynamic status was repeatedly measured during the next 5 min.

The postoperative complications were recorded in both groups after the end of surgery. The volume of totally administered crystalloid and colloid, blood loss, urine volume, and the requirement for vasoactive agents was recorded and analyzed. The threshold of transfusion with packed red blood cells was set at the hemoglobin value <8 g/dL or hematocrit <25%.

Blood samples

The radial arterial blood samples were collected for analysis before OLV (T0, baseline), 30 min (T1) and 60 min (T2) after OLV, 10 min after re-expansion (T3), and the end of the operation (T4) using a blood gas system (Roche Diagnostics GmbH, Mannheim, Germany). The venous blood was sampled from the central venous at T0, T4, and 6 h (T5), 24 h (T6), and 72 h (T7) after the operation, and centrifuged at 2,000 rpm for 15 min at 4 ℃. The collected serum samples were immediately preserved at −80 ℃ for

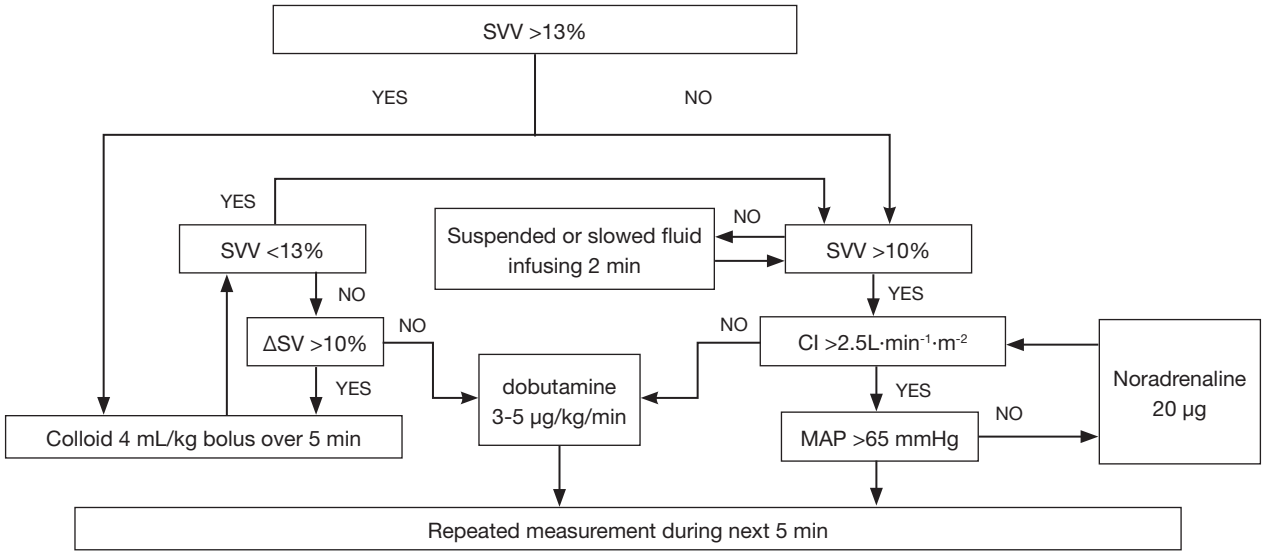

Figure 1 Goal-directed fluid therapy protocol. SVV, stroke volume variation; CI, cardiac index; MAP, mean arterial pressure; ΔSV, the increased SV based on colloid treatment.

subsequent analysis.

Lung function and Qs/Qt ratio

The lung function evaluation including PaO_2/FiO_2, alveolar to the arterial difference of oxygen tension (A-aDO_2), and respiratory index (RI = A-aDO_2/PaO_2) was determined according to the result of the blood gas analysis at the above time-points. The peak airway pressure (Ppeak), plateau airway pressure (Pplat), and dynamic lung compliance (Cdyn) of individual patients at T0–T4 were monitored and obtained directly from the ventilator setting. The Qs/Qt ratio was calculated from the following formula: (CCO_2 – arterial oxygen content)/(CCO_2 – mixed venous oxygen content), the CCO_2 represents the end-pulmonary capillary oxygen content (21).

Postoperative pulmonary-related adverse events such as pneumothorax, pneumonia, pulmonary edema, ALI, and acute respiratory distress syndrome (ARDS) during hospitalization were confirmed based on the chest X-ray characteristics and laboratory examinations according to the American-European Consensus Conference on ARDS guidelines (22).

Inflammatory response

The concentrations of the serum cytokines including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10) were measured by enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (R&D, Minneapolis, MN, USA) according to the manufacturer's instructions.

Short-term outcomes

The length of hospital stay, cardiovascular complications such as hypotension or heart failure (increased cardiac enzyme and NT-proBNP). If age less than 50: NT-proBNP >450 ng/L; if age more than 50: NT-proBNP >900 ng/L), renal dysfunction (creatinine >180 μmol/L) or renal failure (creatinine >450 μmol/L), and gastrointestinal complications after surgery were recorded.

Statistical analysis

To calculate the sample size, we considered a difference of 20 mmHg for PaO_2/FiO_2 between the two groups as reported previously (19). A standard deviation (SD) of 50 mmHg of the means, with a one-sided type I error of 0.05 and compensating 10% cases for potential dropouts; thus, a minimum sample size of 90 patients in each group allowed an 80% statistical power for enrollment in the study.

The statistical analysis was performed using SPSS 16.0 software. Data were assessed for normality using the Kolmogorov-Smirnov test; the continuous normally distributed data were assessed with the mean ± SD and

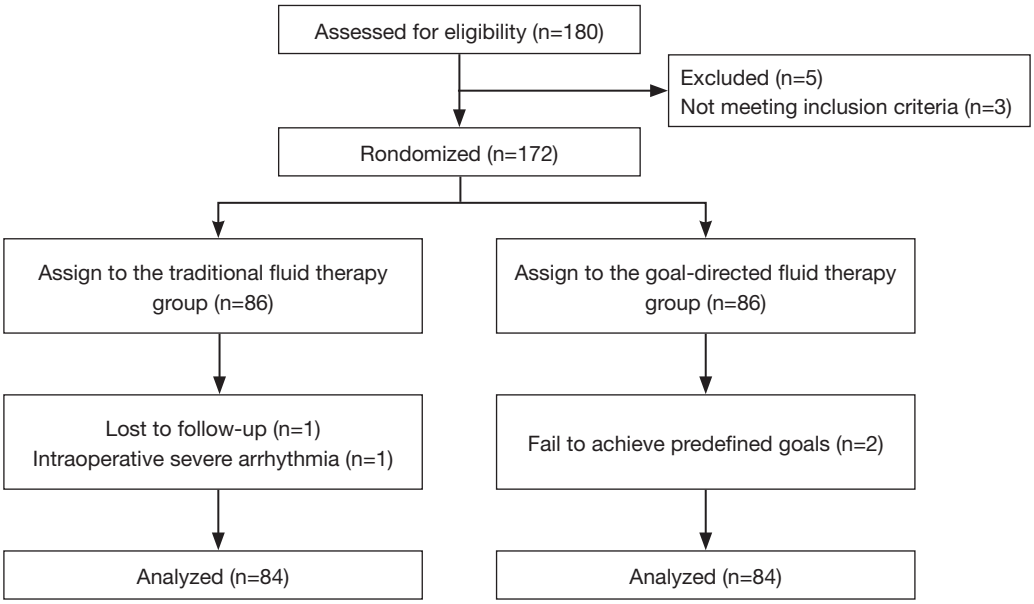

Figure 2 Flow diagram of enrolled patients.

compared using the independent *t*-test. The skewed data were presented as median (range) and compared using the Mann-Whitney U test or Wilcoxon rank-sum test for unpaired and paired results respectively. The categorical data were presented as frequency or percentage and compared using the Fisher's exact test. The concentrations of serum markers were analyzed by repeated-measures ANOVA using Bonferroni correction for *post hoc* analysis. A P-value less than 0.05 was considered statistically significant.

Results

Patient demographics

A total of 180 patients were assessed for inclusion eligibility in this study. Despite preoperative approval, 5 patients were excluded from the data analysis, 3 patients were not meeting inclusion criteria, 1 patient was lost to follow-up, 1 patient had an intraoperative severe arrhythmia, and 2 patients were failed to achieve predefined goals. Thus, 168 were ultimately recruited for analysis and randomly assigned to the GDFR group (group G, n=84) or the conventional fluid therapy group (group C, n=84) as shown in the *Figure 2*. The preoperative demographic and laboratory examination characteristics were summarized in *Table 1*. No statistically significant differences were observed between the two groups with respect to their baseline characteristics. None of the patients experienced adverse surgical events throughout the intraoperative period.

Blood gas analysis, lung mechanics and functions

The intraoperative blood gas analysis and lung mechanics were summarized in *Table 2*. In comparison with the baseline, pH decreased significantly, whereas $PaCO_2$ increased in both groups during OLV. The Ppeak and Pplat in group G were lower than those in group C, whereas the values of Cdyn were higher than those in group G from T1 to T3 with a significant difference between the groups during OLV.

As shown in *Figure 3*, the baseline values of PaO_2/FiO_2, A-aDO_2, RI, and Qs/Qt ratio did not differ baseline between the groups. The values of PaO_2/FiO_2 were distinctly decreased (all P<0.01), whereas the A-aDO_2, RI, and Qs/Qt ratio increased significantly in both groups after OLV was established with significant differences between the groups (all P<0.05).

Intraoperative hemodynamic data

The intraoperative hemodynamic measures, fluid managements and vasoactive drug uses were summarized in *Table 3*. No statistically significant differences were observed

Table 1 Preoperative demographic and laboratory examination characteristics

Characteristics	Group C (n=84)	Group G (n=84)	P value
Age (years)	49±5	49±6	0.52
Gender			0.87
Male	56 (67%)	54 (64%)	
Female	28 (33%)	30 (36%)	
ASA			0.74
I	24 (29%)	27 (32%)	
II	60 (71%)	57 (68%)	
Type of surgery			0.72
Lobectomy	64 (76%)	60 (71%)	
Wedge resection	8 (10%)	11 (13%)	
Segmentectomy	12 (14%)	13 (15%)	
BMI (kg/m^2)	21.7±1.1	21.9±1.2	0.35
Collapsed lung (right side)	46 (55%)	48 (57%)	0.76
Preoperative FVC (% predicted)	93 [85–100]	94 [86–100]	0.69
Preoperative FEV_1 (% predicted)	93 [85–99]	92 [85–99]	0.91
Preoperative FEV_1/FVC (%)	82 [80–85]	82 [79–86]	0.75
Preoperative hemoglobin (g/dL)	12.4±0.9	12.5±1.1	0.38
Preoperative PaO_2 (mmHg)	92 [87–95]	94 [88–97]	0.16
Preoperative $PaCO_2$ (mmHg)	39 [36–43]	39 [34–42]	0.32

Continuous data are presented as mean ± SD or median [interquartile range (IQR)], categorical data are presented as number (proportion). ASA, American Society of Anesthesiologists; FEV_1, forced expired volume in 1 s; FVC, forced vital capacity; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen. BMI, body mass index.

in the duration of OLV and anesthesia between the two groups, whereas the extubating period was significantly earlier in the GDFR group (P<0.01). Dobutamine was used in 9 patients from group G when the CI was less than 2.5 L/min/m^2; however, the bolus of noradrenaline usage in group G was less than that in group C (P<0.01). None of the patients received intraoperative blood transfusion; the total volume of intravenous infusion and crystalloids in group G was significantly lower than that in group C, whereas the volume of colloids was significantly higher than that in group C (all P<0.01). No differences were seen in intraoperative blood losses and urine outputs between the two groups.

As shown in *Figure 4*, The HR and CVP were similar between the two groups at all observational time-points. However, compared to the baseline, the values of MAP were decreased significantly with the initiation of OLV but before the end of surgery in group C. In addition, the values of MAP in group G were greater than those in group C at T1 (P=0.02) and T2 (P=0.03). On the other hand, the values of CI in group C were decreased after OLV begun, and a significant difference was observed between the groups (all P<0.01).

Inflammatory cytokines

As shown in *Figure 5*, no statistically significant differences were observed in the concentrations of serum TNF-α, IL-6, and IL-10 between the two groups at baseline. At later observational time points, these levels were significantly increased as compared to the baseline. In addition, the IL-6 levels peaked at 24 h after the operation, whereas that of TNF-α and IL-10 peaked at 6 h after the operation. However, all of the three did not exhibit any significant

Table 2 Intraoperative blood gas analysis and pneumodynamics

Variables	T0	T1	T2	T3	T4
PH					
Group C	7.39±0.04	7.37±0.05*	7.37±0.04*	7.38±0.04	7.38±0.04
Group G	7.40±0.04	7.38±0.04*	7.38±0.03*	7.39±0.04	7.38±0.04
P value	0.81	0.33	0.25	0.18	0.21
$PaCO_2$					
Group C	40.0±2.2	40.8±2.2*	40.7±2.4*	40.5±2.5	40.5±2.5
Group G	39.9±2.4	40.4±2.5*	40.5±2.7*	40.5±2.8	40.6±2.8
P value	0.87	0.33	0.54	0.98	0.84
Ppeak					
Group C	16.3±2.5	25.2±2.7*	25.6±2.6*	17.8±3.1*	18.0±3.2*
Group G	16.4±2.6	23.4±2.8*#	23.9±2.7*#	17.4±2.7*	17.9±2.7*
P value	0.70	<0.001	<0.001	0.33	0.82
Pplat					
Group C	14.9±2.5	23.6±2.8*	24.2±2.7*	16.4±3.2*	16.6±3.3*
Group G	14.9±2.8	21.9±2.9*#	22.5±2.8*#	15.8±2.8*	16.4±2.8*
P value	0.93	<0.001	<0.001	0.24	0.74
Cdyn					
Group C	41.7±5.3	26.6±4.5*	26.5±4.3*	37.7±4.8*	37.8±5.0*
Group G	42.0±4.3	32.4±5.4*#	31.9±5.6*#	39.4±5.9*#	38.9±6.2*
P value	0.73	<0.001	<0.001	0.04	0.21

Continuous data are presented as mean ± SD. *, P <0.05 versus T0; #, P<0.05 versus group C. PH, potential of hydrogen; PaCO2, arterial partial pressure of carbon dioxide; Ppeak, peak airway pressure; Pplat, plateau airway pressure, Cdyn, dynamic lung compliance; T0, before one-lung ventilation (OLV); T1, 30 min after OLV; T2, 60 min after OLV; T3, 10 min after re-expansion; T4, the end of operation.

difference between groups at obvious time-points.

Short-term outcomes

The short-term outcomes were summarized in *Table 4*. The postoperative incidences of pneumonia, ALI, and nausea and vomiting in group G were lower than those in group C (P=0.02, 0.03, 0.01, respectively). Additionally, the length of hospital stay in group G was significantly lower than those in group C (P<0.01).

Discussion

The principal findings of the clinical study are that SVV-based GDFR protocol improves intraoperative pulmonary oxygenation, lowering the airway pressure and increasing the dynamic lung compliance during surgery. Furthermore, the GDFR protocol stabilized the intraoperative hemodynamics efficiently. Importantly, it can also reduce the length of hospital stay, postoperative nausea and vomiting, and the incidence of postoperative pulmonary complications such as pneumonia and ALI. To the best of our knowledge, this is the first study indicating the protective effect of SVV-based GDFR protocol using FloTrac/Vigileo system on the lung function during OLV.

For patients during thoracic surgery, the purpose of GDFR protocol is not only to reduce the amount of intraoperative fluid infusion, it also wants to optimize the end-organ perfusion and stabilize the hemodynamic status with suitable fluids according to the dynamic parameters. With the chest open via surgical procedures, much of the pressure generated by the ventilator would not be transmitted

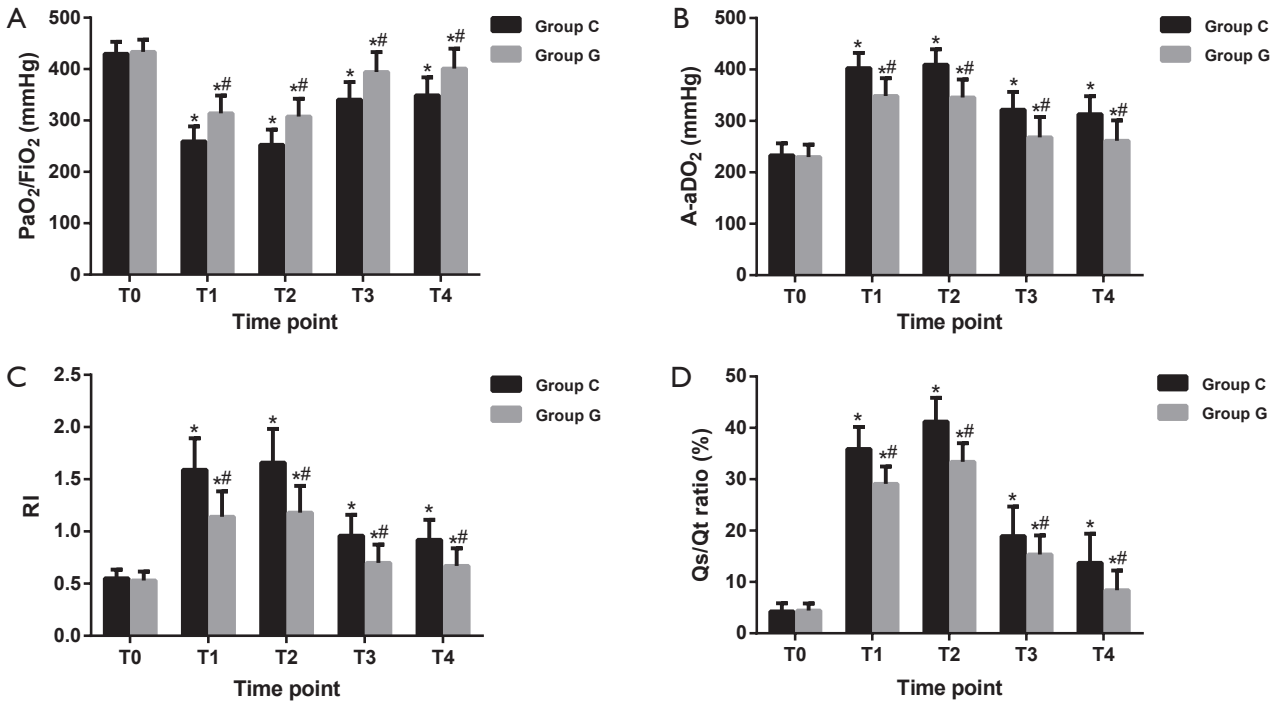

Figure 3 Variables of lung function and Qs/Qt ratio. (A) PaO2/FiO2; (B) A-aDO2; (C) RI; (D) Qs/Qt ratio. Data are represented as mean ± SD. *, P<0.05 versus T0; #, P<0.05 versus group C. A-aDO2, Alveolar to arterial difference of oxygen tension; RI, Respiratory index; T0, before one-lung ventilation (OLV); T1, 30 min after OLV; T2, 60 min after OLV; T3, 10 min after re-expansion; T4, the end of operation.

Table 3 Intraoperative data and fluid management

Factors	Group C (n=84)	Group G (n=84)	P value
Intraoperative data			
Duration of OLV (min)	119±18	118±17	0.67
Duration of anesthesia (min)	144±17	143±18	0.62
Dobutamine (case)	0 (0%)	9 (11%)	<0.001
Noradrenaline (ug)	156±34	120±22	<0.001
Extubation time (min)	20±7	16±5	<0.001
Fluid management			
Crystalloid (mL)	828±281	490±194	<0.001
Colloid (mL)	447±184	625±299	<0.001
Total volume infused (mL)	1275±334	1115±335	0.002
Urine output ($mL \cdot kg^{-1} \cdot h^{-1}$)	2.7±0.7	2.6±0.8	0.57
Estimated blood loss (mL)	72±15	69±15	0.21
Transfusion (u)	0	0	1.00

Continuous data are presented as mean ± SD; categorical data are presented as number (proportion). OLV, one-lung ventilation.

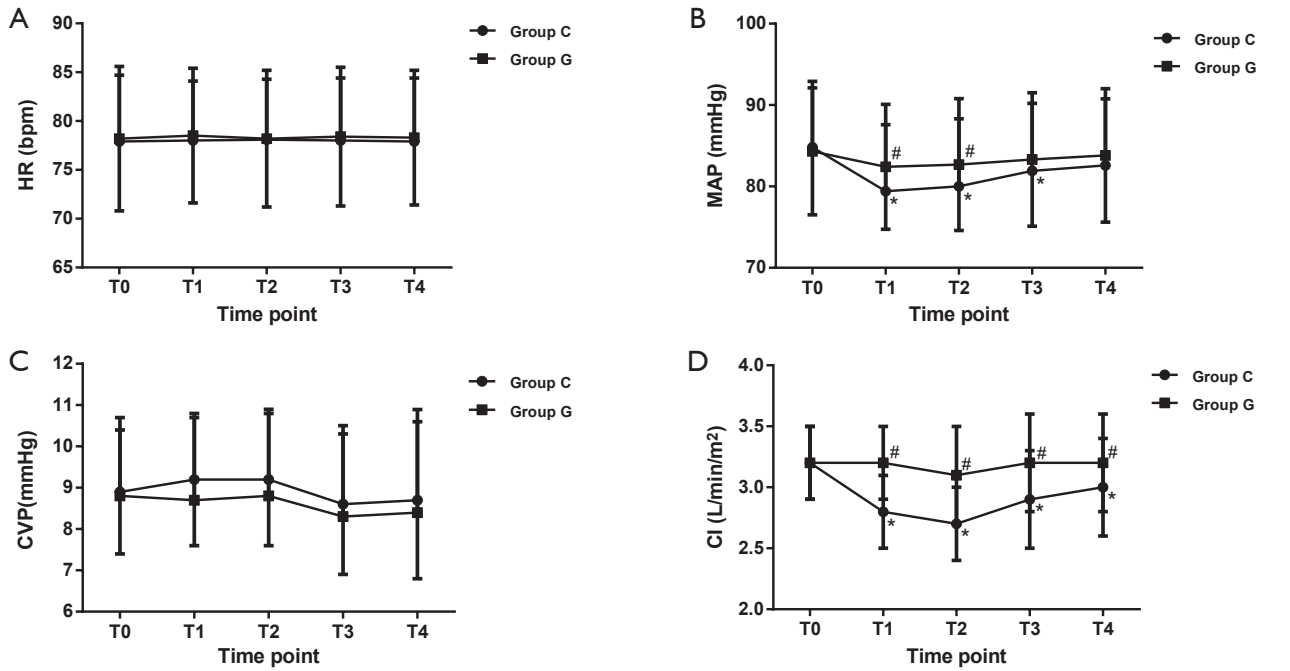

Figure 4 Variables of Intraoperative hemodynamic data. (A) HR; (B) MAP; (C) CVP; (D) CI. Data are represented as mean ± SD. *, P<0.05 versus T0; #, P<0.05 versus group C. HR, heart rate; CVP, central venous pressure.

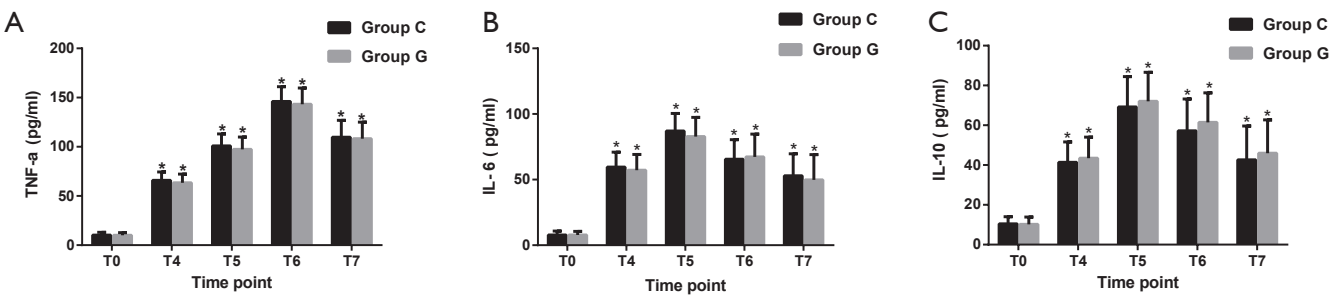

Figure 5 Variables of inflammatory cytokines. (A) TNF-α; (B) IL-6; (C) IL-10. Data are represented as mean ± SD. *, P<0.05 versus T0. TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; IL-10, interleukin-10; T0, before one-lung ventilation (OLV); T4, the end of operation; T5 to T7: 6, 24, 72 h after operation, respectively.

to the pulmonary vessels but rather to the atmosphere, which may result in a decrease in SVV. However, the ventilated lung is actually not open to the atmosphere because its pleura are still intact and the mediastinum also separates that lung from the atmosphere (16). Thus, we believe that SVV could be predictive of fluid responsiveness during OLV. Previous research shown that optimal threshold value of SVV to discriminate between fluid responders and non-responders during OLV was more than 10% (16,17). On the other hand, SVV less than 13% identifies fluid responder patients with high sensitivity and specificity (23,24). Therefore, we decided to use a high cut-off value of SVV between 10% to 13%, in order to retain minimal fluid and maintain the patients on the "dry" side as much as possible. Meanwhile, in the present study, this protocol states that a minimum threshold value of CI >2.5 L/min/m^2 ensures an adequate supply of oxygen to the tissues (25).

In the current study, the indicators including PaO_2/FiO_2, A-aDO_2 and RI were chosen as the primary variables to assess the intraoperative lung function due to its efficiency

Table 4 Short-term outcomes

Outcomes	Group C (n=84)	Group G (n=84)	P value
Cardiovascular complications			
Hypotension (case)	6 (7%)	2 (2%)	0.28
Heart failure (case)	0 (0%)	0 (0%)	1.00
Renal complications			
Renal dysfunction (case)	3 (4%)	1 (1%)	0.62
Renal failure (case)	0 (0%)	0 (0%)	1.00
Pulmonary complications			
Pneumonia (case)	11 (13%)	2 (2%)	0.02
Pneumothorax (case)	4 (5%)	1 (1%)	0.37
Pulmonary edema (case)	3 (4%)	0 (0%)	0.25
ALI (case)	8 (10%)	1 (1%)	0.03
ARDS (case)	1 (1%)	0 (0%)	1.00
Sepsis (case)	0 (0%)	0 (0%)	1.00
Nausea and vomiting (case)	14 (17%)	3 (4%)	0.01
Length of hospital stay (day)	8 [7–9]	7 [6–8]	<0.001

Continuous data are presented as mean ± SD or median [interquartile range (IQR); range], Categorical data are presented as number (proportion). Heart failure was an increased cardiac enzyme and NT-proBNP. Renal dysfunction or failure was an increased creatinine. pulmonary complications were confirmed based on the radiographic infiltrates and laboratory examination. ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

in reflecting intrapulmonary oxygenation and gas exchange (19,26-28). Compared with traditional fluid management, our findings reveal a positive effect of GDFR protocol that alleviate the decreased arterial oxygen content and intrapulmonary gas exchange. Li *et al.* (29) have demonstrated that GDFR protocol could reduce the pulmonary vascular resistance and protect the right ventricular dynamic function in patients with severe pulmonary arterial hypertension. Similarly, we also reveal that GDFR protocol is useful to improve intrapulmonary shunt and decrease venous admixture. Thus, we consider that the possible mechanisms to improve intrapulmonary oxygenation and gas exchange by GDFR protocol is alleviating the pulmonary vascular resistance and minimizing the hydrostatic pressure.

It is well known that mechanical disruption of the alveolar capillary barrier obviously contributes to the lung injury (30). Indeed, rapid fluid infusion might damage the underlying endothelial cells, alveolar epithelial cells, and the surfactant, which may increase barrier permeability, and reduce the alveolar epithelial fluid clearance from the air spaces (31,32). Kapoor *et al.* (33) have provided evidence supporting the effect of GDFR protocol in decreasing the content of extravascular lung water. In the present study, there is a significant improvement in lung mechanics with GDFR protocol, which is potential via alleviating epithelial and endothelial permeability and decreasing pulmonary edema.

The inflammatory response is demonstrated to play a vital role in the pathogenesis of lung injury during OLV (34). However, in this study, we found that patients prescribing to an SVV-guided fluid regimen did not experience a reduction in both pro- and anti-inflammatory response, thereby demonstrating that GDFR protocol is not valuable in adjusting the local or systemic inflammation during OLV, which were somewhat similar to those of Funk *et al.* (35) and Fitzgerald *et al.* (36).

On the other hand, using a crystal liquid supplement may retain most of the crystals in the blood vessels. Besides, hydroxyethyl starch solution was found to be more likely to maintain gastrointestinal microcirculation perfusion and oxygen tension than the crystal (37,38). we therefore decide to use colloid instead of crystalloid in the GDFR protocol.

Although it is not always ideal to use a colloidal solution, as anesthesiologists need to consider various factors, such as nephrotoxic effects (39). However, in the present study, there was no significant difference in the urine volume and postoperative renal complications, which suggested that the bolus of hydroxyethyl starch solution we used not exceed the kidney compensatory. The results of our study also shown that patients undergoing GDFR protocol received a significantly lower amount of intravenous infusion with a different quality of colloids and crystalloids. Meanwhile, the use of vasoactive drugs was also different between groups, which may be the results of different liquid treatment program between groups. Thus, we believe that different types and dose of fluid and vasoactive drugs with the accurate opportunity may prevent the administration of excessive fluid.

Nonetheless, our study harbors several limitations. First, due to the unwillingness of some patients, our study was not evaluated the postoperative intrapulmonary gas exchange and oxygenation based on arterial blood gas. In addition, the long-term effects of SVV-based GDFR protocol on lung function were also lost to follow-up. Second, although we were attempted to exclude the potential influencing factors, some other factors such as social and genetics may continue to interfere the accuracy of the results. Third, this is a single-center research, hence, a multicenter study may alleviate the investigation with respect to the potential of GDFR. Fourth, it is difficult for us to measure the postoperative ARDS based on newer Berlin definition without PEEP after extubation. Therefore, we use the old guidelines of ARDS based on American-European Consensus Conference.

Conclusions

In summary, the current study showed that SVV-based GDFR protocol applied to the patients undergoing OLV might improve the intraoperative pulmonary oxygenation. Moreover, SVV-based GDFR protocol can also reduce the postoperative complications and the length of hospital stay; however, it is not useful in reducing the local or systemic inflammation. Nevertheless, these findings necessitate validation based on a multicenter study.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical statement: This prospective, single-center, randomized clinical study protocol was approved by the Chinese Clinical Trial Registry (No. ChiCTR–IPR-16008288) and the Ethics Committee of Anhui Medical University (Hefei, China). After ethics was approved, all patients were informed of the entire procedure and written informed consents were obtained after a detailed explanation of the study. During the process of research, all treatments were carried out in accordance with the Declaration of Helsinki and the Use Committee of Affiliated Provincial Hospital of Anhui Medical University.

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