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Original Article

Effects of goal-directed fluid therapy on transfusion volume and pulmonary aquaporin 1,5 in a dog model of hemorrhagic shock

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Abstract: Objective: The aim of this study was to investigate the effects of goal-directed fluid therapy (GDFT) on transfusion volume and expression of aquaporin-1 and aquaporin-5 in a dog model of hemorrhagic shock. Methods: A total of 32 Beagle dogs were randomly divided into four groups (n = 8): sham operation (group S), GDFT (group G), central venous pressure (group C), and routine (group R). Dogs in groups G, C, and R were bled from the left femoral artery, using a modified induction of Wiggers shock model. Dogs in the group S continued to receive Lactated Ringer's solution (LRS) and 6% hydroxyethyl starch (HES) at 1 mL/kg·h. After 1 hour of hemorrhagic shock model establishment, dogs in groups G, C, and R underwent GDFT, central venous pressure guide, and routine infusion regimens, respectively, to recover. They were observed for 4 hours and received LRS and HES at an infusion ratio of 1:1. The volume of transfused fluid over 4 hours was recorded. Concomitant expression of aquaporin-1 and aquaporin-5 in lung tissues was quantified. Results: The transfusion volume of group G was greater than that of groups R and C ($P < 0.05$), while expression of aquaporin-1 and aquaporin-5 did not change. Conclusion: GDFT increases transfusion volumes in a dog model of hemorrhagic shock but does not affect expression of aquaporin-1 and aquaporin-5 in lung tissues.

Keywords: Hypovolemic shock, fluid therapy, aquaporin

Introduction

Clinically, surgery is the most common cause of massive blood loss, with approximately 30% of surgery-related deaths caused by blood loss. Massive blood loss is one of the main challenges facing clinicians. Fluid treatment is a critical means of protecting patient life. However, there remains substantial controversy regarding the use of fluid therapy, both at home and abroad. Thus far, there are no generally accepted guidelines [1], although central venous pressure (CVP) has been used widely. One meta-analysis found a weak correlation between CVP and blood volume [2]. However, stroke volume variation (SVV), which reveals the heart-lung interaction during mechanical ventilation, can be used to predict the response of the body to fluid therapy [3, 4]. Previous perioperative solutions have included limited hypotensive resuscitation, aggressive fluid resuscitation, and routine maintenance fluid resuscitation [5].

Limited hypotensive resuscitation, while avoiding an intraoperative fluid overload, often leads to potentially unidentifiable hypovolemia and may cause postoperative organ dysfunction, such as acute renal failure. Aggressive fluid resuscitation can quickly improve fluid volume, but may promote volume overload and pulmonary edema, leading to acute respiratory distress syndrome (ARDS) or pneumonia [6]. Although a routine maintenance transfusion can prevent an apparent perioperative lack of capacity or volume overload, it does not consider individual differences among surgical patients, such as gender, age, and weight. Therefore, it may not meet each patient's changing perioperative fluid demands. In the past ten years, goal-directed fluid therapy

(GDFT) has been proposed for perioperative management of fluids [7]. Hematologic parameters, including gender, age, and body weight, support the use of stroke volume (SV) as a rehydration target for the following purposes: to prevent perioperative hypovolemia [1, 6, 7], maintain hemodynamic stability [4, 6], reduce the duration of mechanical ventilation [7, 8] and postoperative infections [9, 10], improve gastrointestinal function [8, 10, 11], reduce postoperative complications, mortality, and length of hospital stay [4, 12], and further improve patient postoperative outcomes.

However, the impact of GDFT on liquid volume remains controversial. Zheng et al. [13] used GDFT in gastrointestinal surgery to older coronary heart disease patients and found that the total fluids infused of the GDFT group decreased, compared with that of the control group. Moreover, the lengths of overall hospital stay and lengths of stay in the ICU were shortened, while gastric function recovered in the treatment group. However, Pearse et al. [12] found that, although the lengths of hospitalization and the number of postoperative complications were reduced in the GDFT group, the amount of colloid used was significantly more than that in the control group. Benes et al. [4] used SV as a target in a study of 60 patients undergoing elective abdominal surgery. They found that the GDFT group had more colloids than the control group. However, the GDFT patients exhibited more stable perioperative hemodynamics, along with reduced postoperative lactate values and numbers of complications.

Aquaporins (AQP) are a family of water-channel cognate proteins that regulate the entry and exit of water across cell membranes. A total of 11 aquaporins have been found in mammals (AQP 0-10). For example, AQP1 is distributed in alveolar capillaries, lymphatic vessels, and intestinal tissues [14], whereas AQP5 is mainly distributed in alveolar epithelial cells [15, 16]. The main function of aquaporins is to mediate the translocation of free water across the cell membranes, providing a major pathway for the rapid transport of water involved in the secretion and absorption of water, as well as a mechanism to balance water inside and outside of the cell. Therefore, it was speculated that the absorption and distribution of liquids is related to aquaporin expression and activity. In this study, SVV was used to manage GDFT in a dog model of hemorrhagic shock. This study investigated whether GDFT could increase the transfusion volume and affect expression of aquaporin in the lungs of experimental dogs. It was hypothesized that treatment of fluids via GDFT in the context of hemorrhagic shock may result in increased lung water content and upregulation of aquaporin expression.

Materials and methods

Experimental animals and groupings

A total of 32 Beagle dogs (provided by Kunming Medical University Animal Branch) were randomly divided into four groups (n = 8): sham operation (group S), GDFT (group G), central venous pressure (group C), and conventional/routine (group R).

This study was carried out in strict accordance with recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The animal use protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Kunming Medical University.

Surgical preparation of the animals

Beagle dogs were housed in the breeding room for 1 week, eating a designated quantity of food and drinking water freely. Dogs were preoperatively fasted for 12 hours but could drink water during that time. In the animal operating room, dogs were injected with 3% sodium pentobarbital (Shanghai Chemical Reagent Co., Ltd., Shanghai, China) 1 mL/kg by radial intravenous injection and ketamine (Fujian Gutian Pharmaceutical Co., Ltd., Gutian, Fujian, China) 10 mg/kg by intramuscular injections. Dogs were fixed in the stretch neck position on the operating table and underwent endotracheal intubation (internal diameter, 6.5 mm), with a tracheal access anesthesia machine (Draeger; Fabius TIRO, Lübeck, Germany) utilized for machine-controlled breathing. Dogs were administered inhaled oxygen at a concentration of 40% (FiO_2 = 0.4) to achieve a tidal volume (Vt) of 10 ml/kg, a respiration rate (RR) of 25-35 times/minutes, and an inspiratory: expiratory ratio of 1:1.5. Continuous inhalation of isoflurane (Aerrane; Baxter, Guayama, Puerto Rico) was maintained at 1% isoflurane to provide a minimum alveolar effective concentra-

tion (MAC). A compact anesthesia monitor (S/5 Datex-Omeda; GE Healthcare, Helsinki, Finland) was used to maintain the end-tidal carbon dioxide ($EtCO_2$) at 40-45 mmHg, while adjusting the respiratory rate. A urinary catheter for canines (Buster; Eickemeyer Ltd; Copenhagen, Denmark) recorded urine volume.

Right neck and bilateral inguinal areas were trimmed with electric hair scissors to clean the skin. They were then disinfected with iodophor. From the right external jugular vein, an 8Fr triple-lumen central venous (CV) catheter (Arrow, Asheboro, NC, USA) was inserted, with the catheter tip placed into the superior vena cava and atrial junction (an ample depth to monitor the prevailing CVP waveform), to reach the venous corridor. Muscle relaxants were first provided via intravenous injections of vecuronium (Zhejiang Xianju Pharmaceutical Co., Ltd., Xianju, China) 0.2 mg/kg, then continued use of vecuronium 0.2 mg/kg·h to maintain muscle relaxation. An electric heating blanket (Sichuan Mianyang Caihong Electric Heating Blanket Co., Ltd, Mianyang, China) was used to warm each dog to 37-38°C. The bilateral inguinal region was dissected, revealing the bilateral femoral arteries. The right arteries were connected to a pulse indicator continuous cardiac output system (PVPK 2014 L08; Pulsion Medical Systems AG, Munich, Germany) to monitor a variety of parameters, including heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), SVV, and T. The body surface area of beagle dogs was calculated according to the standard formula ($k \times BW^{2/3}$, where $k = 0.112$) [17]. The surface area was then used to calculate CO. Left femoral artery was left for bloodletting and blood collection channels. Group S only underwent intubation and observation, which continued during the observation period. These dogs then received lactated Ringer's solution and 6% hydroxyethyl starch 1 ml/kg·h.

Hemorrhagic shock model

Shock models in groups G, C, and R were made using a modified Wiggers hemorrhagic shock model [18]. Bleeding from the left femoral artery of beagle dogs was performed at a rate of 120 ml/kg·h. Shed blood was collected rapidly into sterile blood bank bags (three-bag collection set; citrate-phosphate-dextrose-adenine; Weigao Products, Weihai, China) until the mean arterial pressure (MAP) was reduced to 50% of the basal value (within 30 minutes). This low MAP lasted for 60 minutes. If MAP exceeded 50% of the baseline during this period, bleeding was continued until MAP reached 50% of baseline.

Fluid resuscitation

After 1 hour of shock, fluid resuscitation was initiated. Crystal fluid and colloidal fluid were administered at a ratio of 1:1. Crystal fluid consisted of Lactated Ringer's solution (LRS, Guangzhou Baxter Medical Products Co., Ltd., Guangzhou, China) and colloidal solution consisted of 6% hydroxyethyl starch 130/0.4 (HES, Voluven; Fresenius Kabi, Graz, Austria). Autologous blood was introduced at a rate of 30 mL/kg·h to maintain hemoglobin (Hb) at 10-11 g/dL. Hb concentrations were measured spectrophotometrically using a single drop of blood (HemoCue Hb 201 + analyzer, Angelholm, Sweden). Re-transfusion of the shed blood was discontinued when the Hb level increased to > 10 g/dL. Hb measurements were performed every 10 minutes during the initial resuscitation, followed by every 2 hours after the target Hb was achieved and maintained. If Hb was not enough, the speed of the transfusion was doubled (60 ml/kg·h) until the hemoglobin reached acceptable levels.

Liquid resuscitation

Groups G, C, and R underwent liquid resuscitation as follows: 1) Group G (GDFT group): If SVV was > 10% during fluid recovery, 4 mL/kg of liquid (LRS and HES, each 2 mL/kg) was transfused. If the target was not reached, the procedure was repeated until the target was reached (SVV < 10%). Adjusting the infusion rate to reach the target, the SVV was maintained at 8-10%; 2) Group R (routine group): rate of fluid [5] = CVE (compensatory intravascular volume expansion) + maintenance administration + deficit + third space + blood loss. CVE: 6 mL/kg (HES); Maintenance administration: calculations of fluid requirements by 4-2-1 Rule (LRS); Deficit: the maintenance fluid requirement × the hours since last intakes (LRS); Third space volume: 2 ml/kg·h (LRS); Loss of blood: autologous blood input was performed to maintain Hb between 10-11 g/dL, MAP maintained at basal level; 3) Group C: During the course of fluid resuscitation, if central venous pressure (CVP) was lower than the basal value, infusion of 4

Table 1. Comparison of weight, length, and experimental time ($\bar{x}$ ± s, n = 8)

Group	Weight (kg)	Length (cm)	Time (h)
S	10.5 ± 2.1	78.2 ± 3.2	7.31 ± 0.39
G	10.8 ± 1.8	78.4 ± 2.9	7.36 ± 0.41
C	10.6 ± 1.5	77.7 ± 4.1	7.56 ± 0.54
R	11.1 ± 1.6	79.1 ± 5.3	7.44 ± 0.52

Data are presented as means ± standard deviation (SD).

mL/kg (LRS and HES, each 2 mL/kg) was administered for 10 minutes, then repeated until the target CVP was achieved (< 10% change from the pre-bleeding baseline). CVP was maintained at < 10% fluctuation by adjusting the LRS and HES infusion rate. Autologous blood infusion was performed to maintain Hb between 10 g/dL and 11 g/L. All dogs were observed for 4 hours after resuscitation.

Measurements

Hemodynamic parameters: This study recorded HR and MAP before the treatment (T0), 1 hour after shock (T1), 2 hours after recovery (T2), and 4 hours after recovery (T4). SV, CI, and SVV of group G were recorded at T0, T1, T2, and T4. CVP of group C was recorded at T0, T1, T2, and T4.

Fluid, blood, and urinary volume parameters

At the end of the experiment, total amounts of fluid resuscitation (crystalloid amount + colloid amount), blood loss, blood transfusion, and urine volume of each group were recorded.

Plasma osmotic pressure

Venous blood was drawn at the end of the experiment (T4) and plasma osmotic pressure of the four groups of dogs was measured using an osmometer (Loser OM815, Germany).

Lung wet weight: dry weight ratio

After the experiment, living dogs were exsanguinated under deep anesthesia (no bleeding was executed under anesthesia). The chest was opened and the left lower lung was removed to determine the ratio of wet/dry weight (W/D) by weighing wet weight and then drying the tissue in an oven (80°C, 48 hours) until the weight was stable. The change of weight % was = 100 × (wet weight-dry weight)/dry weight [18].

Lung histology

The upper left lung was fixed with 10% paraformaldehyde for hematoxylin-eosin (HE) staining.

Reverse transcription polymerase chain reaction (RT-PCR)

Middle and lower lobes of the right lung were harvested for the detection of aquaporins AQP1 and AQP5. AQP1: forward primer: 5'AGCGAGTTCAAGAAGAA3'; reverse primer: 5'GATGAAGACGAAGAGGAT3'; AQP5: forward primer: 5'AACTCGCTCAACAACAAC3', reverse primer: 5'TCGGTGGAAGAGAAGATG3', β-actin: forward primer: 5'AAGTCCATCTCCATCTTC3', reverse primer: 5'ACTCCACAACATACTCAG3'. PCR reaction conditions: 95°C pre-denaturation 2 minutes, 95°C denaturation 15 seconds, 60°C annealing 30 seconds, 72°C extension 30 seconds, for 40 cycles. PCR amplification was performed according to Bio-Rad manufacturer recommendations. The amplified product was separated and imaged by 3% agarose gel electrophoresis, then analyzed by grayscale densitometry.

Western blot

Total protein was extracted, then the BCA method was used to quantify protein concentrations. Primary antibodies were aquaporin-1 (AQP1) (Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA), aquaporin-5 (Santa Cruz Biotechnology Inc., Santa Cruz, CA, US), and β-actin (Wuhan Boston Biological Technology, Wuhan, China). Secondary antibody was goat anti-rabbit (Chemicon International, Temecula, CA, USA). Darkroom exposure was performed, following development with a gel imager (Eastman Kodak, Rochester, NY, USA). The image was measured in grayscale, then the average value was utilized as the final result.

Statistical analysis

SPSS11.0 statistical software was used for analysis. Quantitative data are shown as mean ± standard deviation ($\bar{x}$ ± s). Intra-group comparisons were conducted by multivariate

Table 2. Measurements of HR, MAP, SV, SVV, CI, and CVP at different time points ($\bar{x}$ ± s, n = 8)

Measurement	Group	Basal value (T0)	1 h after shock (T1)	2 h after resuscitation (T2)	4 h after resuscitation (T4)
HR (bpm)	S	145 ± 14	148 ± 23$^{\#}$	143 ± 21	139 ± 19
	G	143 ± 18	170 ± 30$^{\star,\blacktriangle}$	146 ± 19	135 ± 15
	C	141 ± 15	178 ± 27$^{\star,\blacktriangle}$	142 ± 23.1	144 ± 17
	R	139 ± 16	176 ± 25$^{\star,\blacktriangle}$	145 ± 22	146 ± 17
MAP (mmHg)	S	115 ± 11	117 ± 6	117 ± 8$^{\#}$	116 ± 8$^{\#}$
	G	117 ± 11	60 ± 7$^{\star,\blacktriangle}$	130 ± 11$^{\blacktriangle}$	132 ± 14$^{\blacktriangle}$
	C	112 ± 11	57 ± 6$^{\star,\blacktriangle}$	113 ± 8$^{\#}$	113 ± 8$^{\#}$
	R	116 ± 7	59 ± 7$^{\star,\blacktriangle}$	119 ± 8$^{\#}$	117 ± 9$^{\#}$
SV (mL)	G	13.5 ± 3.8	7.6 ± 3.5*	15.7 ± 3.5*	16.5 ± 3.5*
SVV (%)	G	9.2 ± 1.8	28.7 ± 3.6*	9.7 ± 2.1	9.5 ± 1.1
CI (L/min.m^2)	G	1.85 ± 0.3	1.21 ± 0.4*	2.08 ± 0.6*	2.13 ± 0.3*
CVP (cmH_2O)	C	6.83 ± 0.27	4.33 ± 0.41*	6.91 ± 0.45	6.95 ± 0.34

Data are presented as means ± standard deviation (SD). Note: $^{\star}P < 0.05$ v/s T0; $^{\blacktriangle}P < 0.05$ v/s Group S; $^{\#}P < 0.05$ v/s Group G.

Table 3. Results of total amount of fluid resuscitation (crystalloid amount + colloid amount), total amount of blood withdrawn, re-transfused blood amount, and urinary output ($\bar{x}$ ± s, n = 8)

Group	Fluid resuscitation amount (ml)	Crystalloid amount (ml)	Colloid amount (ml)	Blood withdrawn amount (ml)	Re-transfused blood amount (ml)	Urinary (ml)
S	165 ± 23*	84 ± 13*	81 ± 11*	0	0	71 ± 36*
G	964 ± 189$^{\triangle}$	483 ± 95$^{\triangle}$	481 ± 94$^{\triangle}$	372 ± 47$^{\triangle}$	312 ± 38$^{\triangle}$	216 ± 34$^{\triangle}$
C	669 ± 135$^{\blacktriangle,\triangle}$	334 ± 68$^{\blacktriangle,\triangle}$	335 ± 67$^{\blacktriangle,\triangle}$	336 ± 28$^{\triangle}$	305 ± 17$^{\triangle}$	104 ± 21$^{\blacktriangle,\triangle}$
R	591 ± 152$^{\blacktriangle,\triangle}$	295 ± 78$^{\blacktriangle,\triangle}$	296 ± 74$^{\blacktriangle,\triangle}$	351 ± 35$^{\triangle}$	298 ± 23$^{\triangle}$	127 ± 25$^{\blacktriangle,\triangle}$

Data are presented as means ± standard deviation (SD). Note: $^{\blacktriangle}P < 0.05$ v/s Group G; $^{\star}P < 0.01$ v/s Group G; $^{\triangle}P < 0.01$ v/s Group S.

Analysis of Variance (MANOVA) with Repeated Measures Designs. Comparisons between groups were conducted by one-way ANOVA. P < 0.05 is considered to indicate statistical significance.

Results

General data

There were no significant differences in weight, body length, or experiment time among groups (P > 0.05, **Table 1**).

Hemodynamic parameters

In the hemorrhagic shock dog model, the HR and MAP in groups G, C, and R were higher at T1 than at T0 (P < 0.05). In group G, SV and CI were lower at T1 than at T0 (P < 0.05), while SVV was higher at T1 than at T0 (P < 0.05). The CVP in group C at T1 was lower than that at T0 (P < 0.05). At 2 hours after recovery, the HR and MAP of groups G, R, and C gradually decreased to baseline at T2. The SV and CI of group G gradually increased to baseline at T2, whereas SVV gradually decreased to baseline values. CVP gradually increased to baseline. SV and CI at T2 and T4 in group G were higher than at those at T0 (P < 0.05). MAP of group G at T2 and T4 was higher than that of group R (P < 0.05, **Table 2**).

Fluid, blood, and urinary volume parameters

Amounts of transfusion (amount of crystals and colloid) and amounts of urine in group G were greater than those in groups R and C (P < 0.05). The infusion volume of group G (crystal volume and colloidal volume) and urine outputs were greater than those of group S (P < 0.01, **Table 3**).

Plasma osmotic pressure

Plasma osmolality of groups S, G, C, and group R was 296 ± 31 mOsM, 284 ± 41 mOsM, 293 ± 31 mOsM, and 291 ± 37 mOsM, respectively.

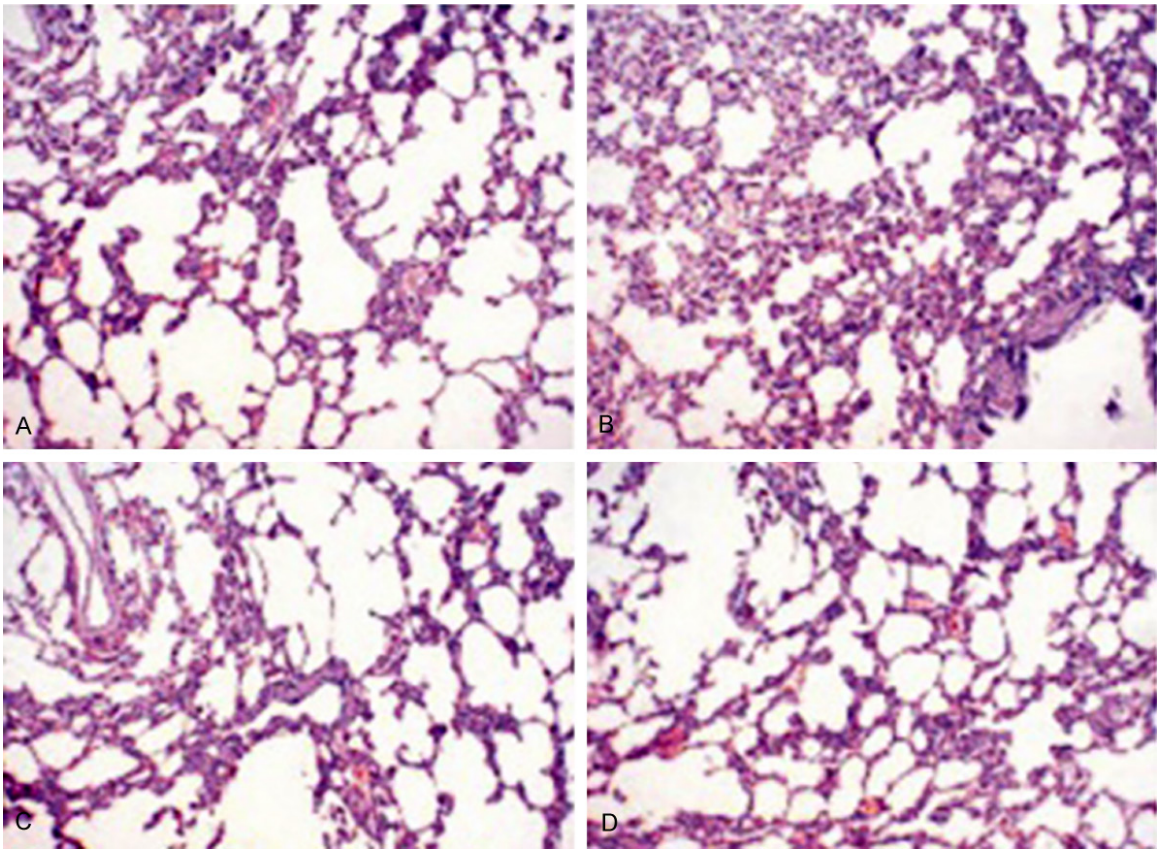

Figure 1. Light microscope image of group S, group R, and group C, which shows that the structure of pulmonary alveoli appeared to remain intact, alveolar septum had no edema, alveolar cavity was clear, and had less inflammatory cells infiltrated (group S, group C, and group R). Group G shows that alveolar septum thickened, some alveolar collapsed, alveolar wall damaged, alveolar cavity had edema fluid, and alveolar cavity was infiltrated more inflammatory cells (group G). Sections were stained with hematoxylin and eosin stain. Original magnification: 4 × 10. A: Group R; B: Group C; C: Group G; D: Group S.

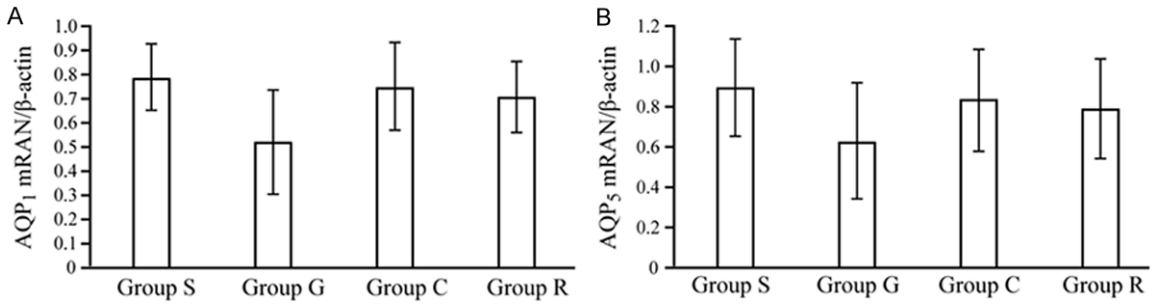

Figure 2. Comparison expression of AQP1 and AQP5 mRNA detected by RT-PCR.

There were no significant differences in plasma osmotic pressure among the groups ($P > 0.05$).

Lung wet weight: dry weight ratio

W/D in groups S, G, C, and R was 4.29 ± 0.17, 4.82 ± 0.15, 4.22 ± 0.12, and 4.36 ± 0.10, respectively. W/D was higher in group G than in groups S, C, and R ($P < 0.05$).

Histopathological studies

Under the light microscope, lung tissues of groups S, C, and R were intact with no alveolar

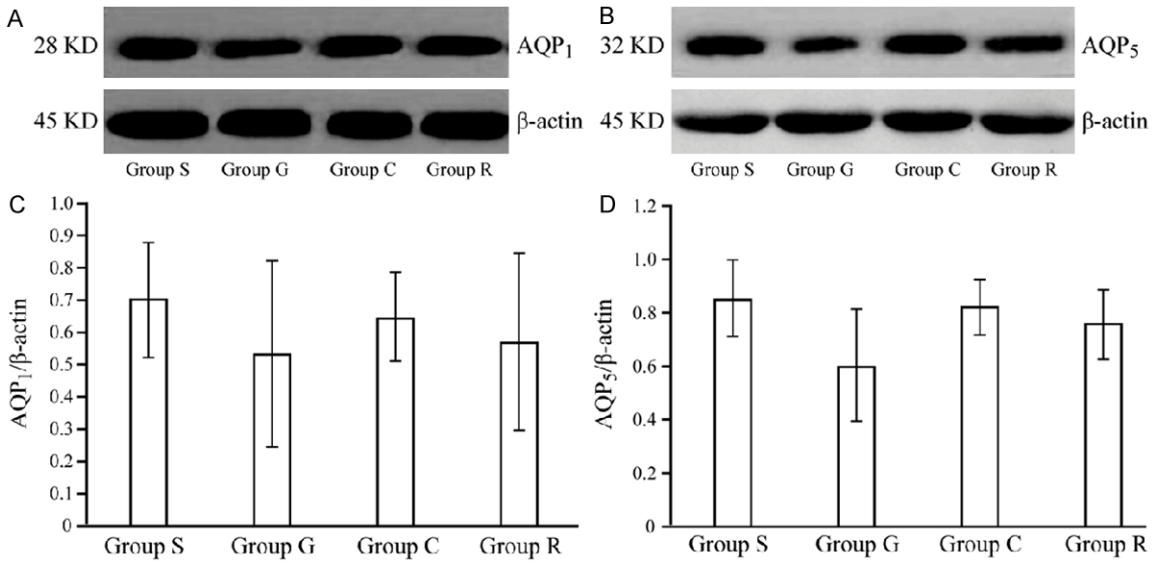

Figure 3. Western blot analysis for AQP1 and AQP5 in the lung tissues. Proteins were extracted and subjected to Western blot analysis with use of polyclonal antibody against AQP1 and AQP5. Data presented are means ± standard deviation (SD). Lanes are as follows: 1, group S; 2, group G; 3, group C; 4, group R.

septum edema, clear alveolar cavity, or mild inflammatory cell infiltration. Group G exhibited a widened alveolar septum, some alveolar collapse, destruction of alveolar wall structure, occasional alveolar edema, and moderate inflammatory cell infiltration (**Figure 1**).

RT-PCR

Quantitative RT-PCR detection of lung tissue AQP1 mRNA and AQP5 mRNA showed that there were no significant differences in AQP1 mRNA and AQP5 mRNA levels among the four groups ($P > 0.05$, **Figure 2**).

Western blot

There were no significant differences in the integral gray values of the Western blots of AQP1 and AQP5 among the four groups ($P > 0.05$) (**Figure 3**).

Discussion

In this study, SVV was used to guide infusion therapy in a dog model of hemorrhagic shock. To determine whether GDFT could increase the transfusion volume in these dogs and the concomitant expression of aquaporin, it was hypothesized that GDFT would increase lung water content and upregulate aquaporin expression.

However, present results revealed that GDFT results in increased transfusion volume and lung water content in the dog model of hemorrhagic shock but does not affect expression of aquaporin.

Traditional perioperative transfusions use routine maintenance fluid resuscitation. The transfusion volume is based on preoperative fasting, physical requirements of no liquid intake, loss of gastrointestinal preparation, and intraoperative bleeding, as well as other parameters. The main goal is to maintain perioperative blood pressure, heart rate, and urine volume. Most fluid volumes are pre-set, without considering individual differences, such as gender, age, concurrent disease, and circulatory function status. Blood pressure, heart rate, and urine output cannot reflect mild perioperative capacity deficiencies, due to anesthesia, surgical stress, and many other factors. Therefore, traditional transfusions cannot achieve the desired capacity status. With the introduction of the concept of “GDFT” in the past decade, this individualized infusion strategy has attracted more attention. The target of GDFT is improved perioperative hemodynamic parameters (such as stroke volume and cardiac output), rather than maintaining the output of the target of surgery or ensuring that oxygen reaches a fixed value. The program is based on indi-

vidual needs, rather than pre-set volumes, which may help to prevent perioperative volume deficiencies. Westphal et al. [19] suggested that GDFT is a personalized infusion solution with the potential to become the main perioperative infusion strategy in improving the prognosis of high-risk surgery patients.

CVP is a commonly used indicator to guide fluid therapy, although some studies have suggested that CVP is not sufficiently accurate to guide liquid therapy [2, 20, 21], especially for critical patients [22]. In this experiment, as shown by the PiCCO system, group G exhibited hypovolemia at 1 hour after hemorrhagic shock and SVV increased to the highest value. SVV decreased gradually with liquid resuscitation and finally returned to normal within 2 hours. SVV values remained normal from T2 to T4, indicating that the infusion was ample, with stable blood pressure. Therefore, with the lack of blood volume, SVV increased, since the Frank-Starling curve of the left ventricle exhibited an ascending curve, indicating that the changes in SV were more significant due to mechanical ventilation, than due to normal blood volume. When the blood volume was sufficient, the Frank-Starling curve of the left ventricle was stable and SV changes were lessened.

This study found that the infusion volume in group G (964 ± 189 mL) was higher than that in groups G (669 ± 135 mL) and C (591 ± 152 mL), probably because of the maximized stroke volume in the GDFT. Thus, more fluid was needed than predicted by CVP guided and pre-set therapy, so the SV and CI were higher than those before surgery at T2 and T4. Additionally, MAP, renal perfusion, and urine volumes were higher. However, the W/D in group G (4.82 ± 0.15) was higher than that in groups S (4.29 ± 0.17), R (4.36 ± 0.10), and C (4.22 ± 0.12) ($P < 0.05$), indicating that the water content of lung tissues in group G was higher than that in groups S, R, and C. In group G, pathological analysis revealed that the alveolar septum was widened and edema fluid was occasionally seen in the alveoli, indicating that targeted fluid therapy may increase the risk of pulmonary edema during fluid resuscitation in this model of hemorrhagic shock.

Present results were consistent with those of Kelm et al. [23]. They retrospectively analyzed 405 patients with infections or septic shock that were admitted to the intensive care unit and underwent GDFT. They found that GDFT caused fluid overload in the patients. In this study, “acute hemorrhagic shock” and transfusions of blood in the animal model resembled the clinical situation.

After hemorrhagic shock, 40% of model mice develop pulmonary microvascular permeability and leakage of intravascular fluid into the interstitial lungs [7]. Previous studies have focused on changes in pulmonary vascular permeability. The role of aquaporin (AQP) fluid transport in lung injuries and pulmonary edema is still not known. This study aimed to observe whether GDFT could affect the expression of aquaporin in the lungs of a dog model of hemorrhagic shock.

Since 1988, when Peter discovered the first aquaporin on the erythrocyte membrane, 11 aquaporins have been found in mammals (AQP0-10). AQP1 is mainly expressed on the capillaries, lymphatic vessels, and alveolar capillary endothelial cells in the airways, while AQP5 is located on the alveolar surface of alveolar type I epithelial cells. The main function of AQP1 is to transfer water into the bronchial and perivascular tissue, whereas AQP5 mainly functions to remove alveolar water.

Some experiments have confirmed that [24, 25] there is a decrease in AQP expression and activity in alveolar epithelial cells and capillary endothelial cells during acute lung injuries. Recent studies have shown that AQP1 and AQP5 are involved in the pathophysiology of pulmonary edema after multiple lung injuries [26, 27].

Studies have shown that the regulation of aquaporin factors includes hormones, neurotransmitters, and cytokines. Hoffert et al. [28] reported that AQP5 expression can be induced under hyperosmotic pressure, which requires the activation of the extracellular signal-regulated kinase (ERK). The osmolality of the HES used in this study was 308 mOsM, whereas that of LRS was 272 mOsM. To compare the transfusion volume and aquaporin in the present dog model of hemorrhagic shock in the same conditions, the ratio of LRS to HES was fixed at 1:1. Results showed no significant differences in osmotic pressure at 4 hours after resuscitation in the three groups. This may

explain why the expression of AQP1 and AQP5 in group G was not significantly different from that in groups S, R, and C.

The present study had a limitation. This study only used an LRS and HES ratio of 1:1. Thus, different ratios of these solutions may yield different results.

In summary, GDFT led to an increase in infusion and lung water content in a dog model of hemorrhagic shock, but did not affect expression of aquaporin in dog lung tissues.

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Disclosure of conflict of interest

None.

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