

Effects of Shen-fu injection on lung injury in a porcine model of hemorrhagic shock

Qiang Zhang^a, Zhao Liu^b, Gu Wei^{c,*}, Bo Liu^{b,*}

Abstract

Background: Since it remains unclear whether Shen-fu injection (SFI) could be used in hemorrhagic shock (HS), this study aimed to explore the effects of SFI on lung injury caused by HS in a porcine model.

Methods: After HS induction, 32 pigs were allocated using simple randomization to four groups (n = 8 each): Group I (no resuscitation), Group II (shed blood reinfusion), Group III (reinfusion + saline 3 mL/kg), and Group IV (reinfusion + Shenfu injection 3 mL/kg). At 6 hours after HS, lung tissue was collected to measure IL-6, IL-8, IL-4, and IL-10 by ELISA, and to evaluate apoptosis by immunohistochemistry and transmission electron microscopy. Tissues from non-survivors were obtained at the time of death and analyzed when available.

Results: Of the 32 randomized animals, 23 survived to 6 hours (Group I, 4/8; Group II, 6/8; Group III, 6/8; Group IV, 7/8). Cytokine analysis revealed that group IV exhibited significantly reduced levels of proinflammatory cytokines, including IL-6 and IL-8, concomitant with elevated concentrations of anti-inflammatory cytokines, specifically IL-4 and IL-10 ($P < 0.05$). Additionally, group IV demonstrated significantly elevated superoxide dismutase enzymatic activity, alongside enhanced $\text{Na}^+\text{-K}^+\text{-ATPase}$ and $\text{Ca}^{2+}\text{-ATPase}$ activities, coupled with markedly reduced malondialdehyde levels ($P < 0.05$). Immunohistochemical analysis revealed downregulated caspase-3 expression and upregulated Bcl-2 expression in group IV, collectively indicating attenuated apoptotic activity. Ultrastructural examination of pulmonary tissues further demonstrated that SFI administration effectively ameliorated alveolar edema, hemorrhage, and inflammatory cell infiltration, while concurrently mitigating epithelial cell apoptosis and mitochondrial injury relative to the other experimental groups.

Conclusion: Among animals surviving to the 6-hour assessment, SFI was associated with differences in selected inflammatory, oxidative-stress, apoptosis, and histological markers. Because of differential mortality, small outcome-specific sample sizes, and limited quantitative histology, these findings should be considered exploratory and do not establish improved survival or hemodynamic benefit.

Keywords: Hemorrhagic shock, Lung, Shen-fu

Introduction

Hemorrhagic shock (HS) is characterized as a hypovolemic shock, following severe blood loss, cellular-level manifestations may reflect inadequate oxygen delivery.^[1] Traumatic disease is a common cause

of death and disability in the young population.^[2] HS accounts for approximately 50% of posttrauma deaths,^[3] which can lead to multiorgan ischemia-reperfusion injury, thereby triggering a systemic inflammatory response.^[4] Although resuscitation therapy using fluids and blood products remains crucial for treatment, aggressive fluid resuscitation may result in multiple complications,^[5] including acute lung injury (ALI).^[6] As the severity of HS classes advanced, a progressive decline in left ventricular function was observed. Concurrently, the coronary arteries exhibited an increased proportion of retrograde flow during diastole, accompanied by a progressively more negative total coronary blood flow.^[7]

Recently, there has been an increase in research focusing on hemodynamic and oxygen metabolism parameters in patients with HS. A previous study based on a porcine model of HS demonstrated that the mean aortic pressure was significantly lower than that in the sham-operated group, while the heart rate was significantly higher.^[8] Many studies have concentrated on mitigating lung injury and have proposed novel drugs to enhance hemodynamic parameters. Improving ALI contributes to maintaining tissue perfusion.^[9]

Shen-fu injection (SFI) is extracted from Shen-fu Decoction and has been used in China for the treatment of cardiac diseases for approximately 800 years.^[10] Its main constituents are ginsenosides and aconitum alkaloids.^[11, 12]

A prior investigation demonstrated that SFI substantially enhanced hemodynamic parameters and effectively attenuated inflammatory responses during the initial phase of fluid

QZ and ZL contributed equally to this article.

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

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resuscitation in patients with septic shock.^[13] Additionally, the study by previous study demonstrated that SFI could mitigate post-resuscitation lung injury.^[14] However, it remains unclear whether SFI can protect lung function in HS. The present study was designed to elucidate the impact of SFI in a porcine model of HS, with the hypothesis that SFI would optimize hemodynamic parameters and mitigate pulmonary injury.

Materials and methods

The experimental protocol was approved by the Animal Experiment Ethics Committee of Capital Medical University. All experiments were carried out in accordance with the principles outlined in the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. Animal experiments do not require written informed consent. In this study, 32 inbred Landrace male pigs (age: 7 ± 1 months) were utilized.

The pigs were fasted overnight before the experiment but allowed free access to water. They were administered intramuscular ketamine (0.5 mg/kg) and intravenous propofol (1 mg/kg). During the maintenance phase of anesthesia and analgesia, continuous intravenous infusions of propofol (9 mg/kg/h) and fentanyl (1 µg/kg/h) were administered. Tracheal intubation was performed using an endotracheal tube with an internal diameter of 6.5 mm. The pigs were placed on a Servo 900c volume-controlled ventilator manufactured by Siemens AG, Germany, with the tidal volume, inspired oxygen concentration, inspiration/expiration ratio, and positive end-expiratory pressure set at 8 mL/kg, 0.21, 1:2, and 5 cm H₂O, respectively. The respiratory rate was adjusted based on the end-tidal carbon dioxide partial pressure.

The surgeons sequentially exposed the right femoral artery and the right external jugular vein. A 6F catheter (Edwards Life Sciences, Irvine, CA) was inserted into the thoracic aorta via the right femoral artery for arterial blood sampling; simultaneously, the mean arterial pressure (MAP) was recorded using a pressure transducer (Biosensors International Corp., Singapore, Singapore). A 7F Swan-Ganz catheter (Edwards Life Sciences) was inserted through the right external jugular vein to measure right atrial pressure and cardiac output. We monitored electrocardiograms and hemodynamic parameters using a multi-parameter monitor.

Experimental protocol

After the surgical procedure was completed, we recorded the baseline data of the pigs. The method for establishing an HS animal model referred to previous literature.^[15] Briefly, rapid blood withdrawal was performed through an arterial sheath to reduce the MAP to 40 mm Hg within 10 minutes and maintain it at the level of 40 ± 3 mm Hg for 1 hour. The withdrawn blood was collected and stored in a blood storage bag (S-400, Sichuan Nightingale Biological Products Co., Ltd., Chengdu, Sichuan, China). Depending on the situation, if the MAP was >44 or <36 mm Hg, blood was reinfused or a crystalloid solution was administered as appropriate.^[15]

After 60 minutes of HS, this time point was designated as 0 hour after HS. Animals were allocated using simple randomization based on a computer-generated sequence prepared by an independent statistician. Allocation was concealed until assignment. Blinding was strictly applied during specimen detection and data analysis. The technicians responsible for sample measurement and the researchers conducting

statistical analysis were blinded to group allocation throughout the experiment, which effectively avoided potential measurement bias and observer bias. After 60 minutes of HS, the time was set as 0 hour after HS and 32 animals were randomly divided into the following groups based on the resuscitation methods as follows: group I (n = 8, no resuscitation), group II (n = 8, resuscitated with shed blood), group III (n = 8, resuscitated with shed blood and saline at a dose of 3 mL/kg), and group IV (n = 8, resuscitated with shed blood and SFI at a dose of 3 mL/kg). SFI was intravenously administered at a dose of 3 mL/kg, which was chosen based on a previous study.^[16] Subsequently, all the pigs received basal crystalloid infusion at 10 mL/kg/h. They were euthanized with intravenous propofol (3 mg/kg), followed by potassium chloride (10 mL of 10 mol/L) 6 hours after HS. This method fully complies with international guidelines for humane euthanasia of laboratory animals.

Measurements of cytokines concentrations

The lungs were immediately removed, and cytokine levels were analyzed. Specifically, all lung tissue specimens were collected from the middle lobe of the right lung in all experimental animals. Interleukin (IL)-6 (ELP-IL6-1, RayBiotech Life, Inc., Peachtree Corners, GA), IL-8 (ELP-IL8-1, Raybiotech), IL-4 (ELP-IL4-1, Raybiotech), and IL-10 (P-1000, R&D Systems, Minneapolis, MN) levels were measured with an enzyme-linked immunosorbent assay using porcine cytokines.

Moreover, we measured Malondialdehyde (MDA) levels (A-003-1-2, Nanjing Jiancheng Institute of Biology, Nanjing, Jiangsu, China), Na⁺-K⁺-adenosine triphosphatase (ATPase) activity (A-070-2-2, Nanjing Jiancheng Institute of Biology) Ca²⁺-ATPase activity (A-070-4-2, Nanjing Jiancheng Institute of Biology), and superoxide dismutase (SOD) enzyme activities (A-001-3-1, Nanjing Jiancheng Institute of Biology).

Measurement of RNA expression using real-time qualitative polymerase chain reaction

Total RNA of tumor necrosis factor (TNF)-α and IL-1β in fresh lung samples was measured. Moreover, we performed RNA reverse transcription using the Revert Aid First Strand cDNA Synthesis Kit, which was purchased from Tiangen Biotech Co., Ltd., Beijing, China. Real-time qualitative polymerase chain reaction was performed using an ABI Prism 7500 instrument (Applied Biosystems, Foster City, CA, USA). Table 1 lists the RNA primer sequences. Gene transcription was quantified through comparison using a standard curve and standardized β-actin transcription. The 2^{-ΔCt} method was used as previously described. All samples were inspected, and the trials were performed in triplicate.

Table 1
The RNA Primer Sequences

Gene	S	A
ACTIN	TGGTCTCTGGGCTCTGTAAGGC	TGATGCCGTGTTCTATTGGGT
TNF-α	GCCCAAGGACTCAGATCATCG	GGCATTGGCATACCCACTCT
IL-1β	AAGGAAGTGATGGCTAACTACGGT	GGAGGGATTCTTCATCGGCT

ACTIN, actin; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha.

Western blot

We extracted proteins from the lung tissues of each group. Samples were quantified using the bicinchoninic acid method and subsequently loaded onto sodium dodecyl sulfate-polyacrylamide gel electrophoresis (Servicebio, Wuhan, China); subsequently, they were transferred onto a polyvinylidene fluoride membrane (Millipore, IPVH00010). The membranes were incubated using primary antibodies at 4 °C overnight. We used the following antibodies: anti-TNF alpha (1:1000, cat. Ab4193, Abcam, Cambridge, UK), anti-IL-1 beta (1:1000, Ab193852, Abcam, Cambridge, UK), and ACTIN (1:1000, GB12002, Servicebio). Subsequently, the membranes were incubated using a secondary antibody (1:3000). Bands were detected using an imaging system (LI-COR Biosciences, Lincoln, NE). Western blots were measured using AlphaEaseFC software (alphaEaseFC, Alpha Innotech, San Leandro, CA, USA); further, protein expression was normalized to ACTIN, as verified from the original uncropped membranes.

Immunohistochemistry staining

Immunohistochemistry staining was performed using a standard protocol, including polyclonal anti-Bax (50599-2-Ig, Proteintech, Rosemont, IL), anti-Bcl-2 antibodies (12789-1-AP, Proteintech), and anti-caspase-3 (19677-1-AP, Proteintech) at 1:10,000 dilution. Subsequently, we added HRP-conjugated Affinipure Goat Anti-Rabbit IgG(H+L) secondary antibody at a 1:1000 dilution. The staining results were observed using CX41 optical microscope (Olympus, Tokyo, Japan).

Ultrastructural analysis

A lung tissue analysis was performed as previously described. We observed ultrastructural changes using light microscopy and transmission electron microscopy (JEM-1400; Tokyo, Japan) at 200 × magnification.

Statistical analysis

With $\alpha = 0.05$, and power = 0.80, a minimum of 7 pigs per group (total $n = 28$) was required detect the intergroup difference based on pilot study data. To account for anticipated mortality during HS induction, we enrolled 8 pigs per group (total $n = 32$). Continuous variables were assessed for

normality using the Shapiro–Wilk test and for homogeneity of variance using Levene’s test. Data were expressed as mean $\pm$ standard deviation. Differences among groups were analyzed using one-way analysis of variance, followed by Tukey’s Honestly Significant Difference post hoc test for pairwise comparisons.

Discrete variables, including the 6-hour survival rate, were compared using the Kaplan–Meier method with log-rank test. Statistical significance was set at $P < 0.05$. All statistical analyses were conducted using IBM SPSS Statistics, version 20.0 (IBM SPSS Inc., Chicago, IL). Statistical significance was set at $P < 0.05$.

Results

Survival outcomes of each group

Of the 32 randomized animals, 23 survived to the 6-hour end-point (Group I, 4/8; Group II, 6/8; Group III, 6/8; Group IV, 7/8). The SFI group showed a non-significantly higher survival rate than the other groups; however, the overall difference among the four groups was not statistically significant (log-rank test, $P = 0.301$), with mean survival times of 4.23 h (95% CI: 2.88–5.59) for Group I, 4.88 h (95% CI: 3.15–6.24) for Group II, 5.34 h (95% CI: 4.49–6.19) for Group III, and 5.75 h (95% CI: 5.29–6.21) for Group IV (Fig. 1). Necropsy and tissue sampling were performed immediately upon death for non-surviving animals. Biochemical and histological analyses were restricted to animals with available specimens. Missing data arising from premature death were not imputed, and sample sizes for each biochemical and histological outcome are reported individually.

Cytokines concentrations

Shapiro–Wilk test showed IL-6, IL-8, IL-4, IL-10, SOD, MDA, Na^+/K^+ -ATPase activity, and Ca^{2+} -ATPase activity satisfy normal distribution. As shown in Table 2, compared with the other groups, group IV showed a significant decrease in the levels of the proinflammatory cytokines IL-6, IL-8, as well as a significant increase in the levels of anti-inflammatory cytokines IL-4 and IL-10 ($P < 0.05$). Group IV showed higher SOD enzyme activities, Na^+/K^+ -ATPase activity, and Ca^{2+} -ATPase activity ($P < 0.05$), as well as significantly lower MDA levels than the other groups.

Protein marker expression and real-time qualitative polymerase chain reaction of tumor necrosis factor- α and interleukin-1 β

As shown in Figure 2, real-time qualitative polymerase chain reaction showed decreased RNA expression of TNF- α and IL-1 β in group IV than in groups I, II, and III ($P < 0.05$); however, there was no significant difference between group II and group III ($P > 0.05$).

Western blot (Fig. 3) analysis revealed decreased protein expressions of TNF- α /ACTIN and IL-1 β /ACTIN, respectively, in group IV than in groups I, II, and III ($P < 0.05$); however, there was no significant difference between group II and group III ($P > 0.05$).

Immunohistochemistry assay

Immunohistochemistry staining results showed decreased caspase-3 levels in group IV than in the other groups. Additionally,

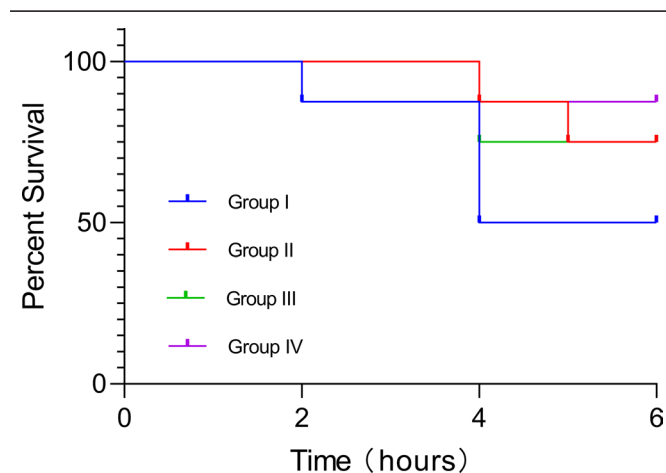


Figure 1. K–M survival of each group. K–M analysis results showed that SFI prolonged survival time, but there was no difference in the survival rate of each group (Log-rank, $P = 0.301$). SFI, Shen-fu injection.

Table 2
Cytokines, Na⁺-K⁺-ATPase and Ca²⁺-ATPase activities, and malondialdehyde content in lung tissue at 6 hours after hemorrhagic-shock resuscitation

Group	IL-6 pg/mL	IL-8 pg/mL	IL-4 pg/mL	IL-10 pg/mL	SOD (NU/mg)	MDA (mol/g)	Na ⁺ -K ⁺ -ATPase (U)	Ca ²⁺ -ATPase (U)
Group I	279.19±4.29	108.81±5.12	25.66±3.18	30.28±3.42	28.73±3.41	4.27±0.42	1.57±0.18	2.70±0.18
Group II	254.27±3.81*	90.17±3.72*	29.26±2.25*	36.57±3.09*	37.26±2.18*	3.28±0.19*	1.98±0.20*	3.65±0.32*
Group III	253.28±2.97*	89.94±4.52*	31.43±3.14*	37.21±2.93*	38.82±3.23*	3.29±0.24*	2.02±0.32*	3.72±0.19*
Group IV	231.28±4.92***	76.93±6.12***	39.16±2.28***	45.17±2.19***	49.86±3.42***	2.47±0.51***	2.84±0.27***	4.97±0.29***

Values are mean ± SD.
**P* < 0.05 vs. group I.
***P* < 0.05 vs. group II.
****P* < 0.05 vs. group III.
Ca²⁺-ATPase, calcium adenosine triphosphatase; IL, interleukin 6; MDA, malondialdehyde; Na⁺-K⁺-ATPase, sodium-potassium adenosine triphosphatase; SD, standard deviation; SOD, superoxide dismutase.

Bcl-2 was upregulated. Bax expression was downregulated in group IV (Fig. 4).

Ultrastructural changes in the lungs

Examination of ultrastructural changes in lung tissues at 200× revealed that SFI (group IV) alleviated alveolar edema, alveolar hemorrhage, and inflammatory cell infiltration compared with the other groups. Moreover, SFI (group IV) decreased epithelial cell apoptosis, reduced the number of lamellar bodies with vacuole-like structures, and reduced mitochondrial damage compared with groups I, II, and III (Fig. 5).

Discussion

This study showed that SFI could decrease cytokine inflammatory response, and suppress pulmonary apoptosis in a porcine HS model.

HS is the main cause of early death after severe injury.^[17] In America, HS causes >60,000 deaths annually.^[18] Acute massive blood loss induces excessive production of inflammatory cytokines, which causes pulmonary dysfunction. Inflammation is frequently related to low oxygen levels. Oxygen supply to cells may regulate oxygen exchange and microcirculation.^[19] Therefore, HS is associated with a low survival rate. SFI may scavenge free radicals, inhibit inflammatory mediators, suppress cell apoptosis, and regulate the host immune response.^[20]

HS triggers a systemic inflammatory response and the release of C5a.^[12] Studies have shown that proinflammatory mediators may lead to hemodynamic instability, organ dysfunction, and coagulation abnormalities.^[21] Jin et al.^[22] reported that SFI reduced complement and cytokine levels compared to the control group. SFI improved survival rate and cardiac function of septic mice mainly by suppressing inflammation and apoptosis.^[23] Therefore, SFI may improve hemodynamics and oxygen dynamics by regulating complement and cytokine levels.

Lactate is an important marker for hemodynamics and could allow the evaluation of the adequacy of fluid resuscitation for HS.^[24] Lactic acid clearance reflects the capability of tissue hypoxia and acidosis, which may increase the survival chances. Moreover, metabolic acidosis is indicative of high mortality

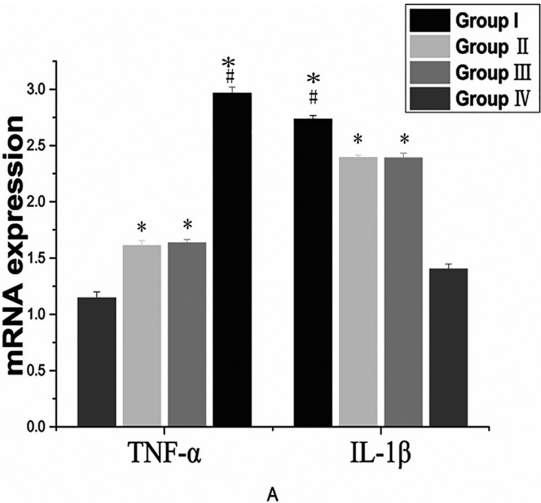


Figure 2. Measurement of RNA expression using real-time quantitative polymerase chain reaction. IL, interleukin; TNF, tumor necrosis factor.

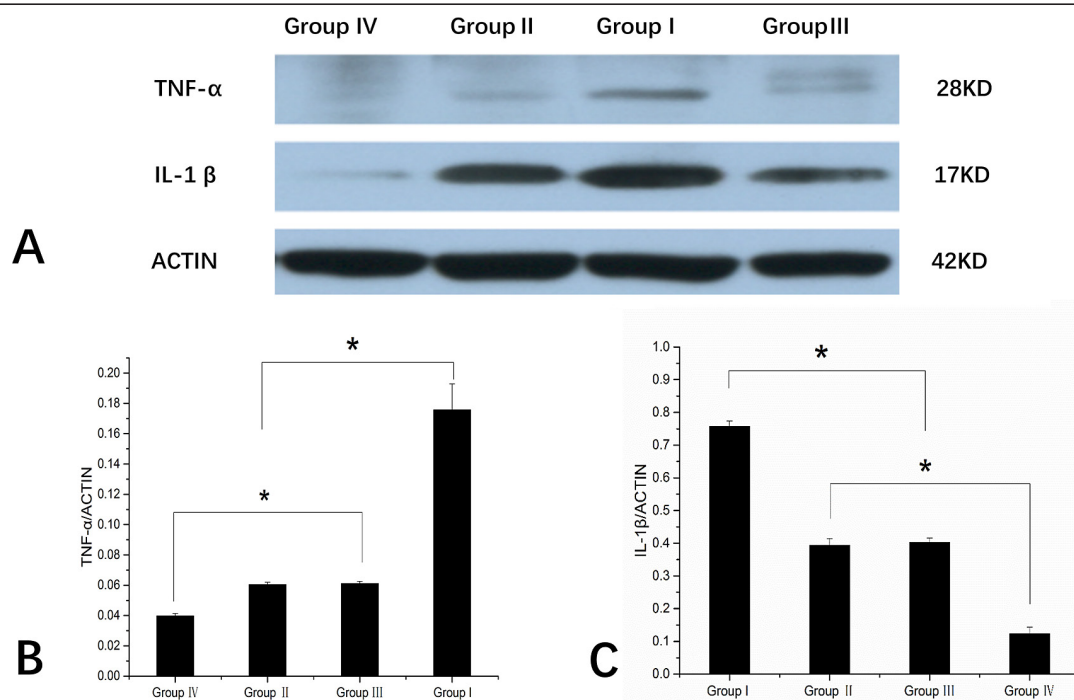


Figure 3. Expression of proinflammatory cytokines in different experimental groups. (A) Representative Western blot analysis showing the protein expression levels of TNF-α (28kDa), IL-1β (17kDa), and the loading control ACTIN (42kDa) in group I, group II, group III, and group IV. (B) Quantitative analysis of TNF-α protein expression, normalized to ACTIN. Data are presented as mean ± SEM. * $P < 0.05$ indicates a statistically significant difference between the indicated groups. (C) Quantitative analysis of IL-1β protein expression, normalized to ACTIN. Data are presented as mean ± SEM. * $P < 0.05$ indicates a statistically significant difference between the indicated groups. IL, interleukin; SEM, standard error of the mean; TNF, tumor necrosis factor.

among critically ill patients, especially those with tissue hypoperfusion and hypoxia.^[25] In patients with septic shock, SFI can decrease lactate levels.^[26]

Excessive release of inflammatory factors after HS is among the key ALI causes.^[27] Specifically, it can inhibit the cascade amplification of inflammation and is an important treatment target.^[28] SFI can suppress the NF-κB pathway and inhibit endotoxin-induced pulmonary inflammation.^[29] IL-6 and IL-8 are crucially involved in inflammation; moreover, IL-4 and IL-10 are important anti-inflammatory mediators. As aforementioned, HS significantly increased IL-6 and IL-8 levels as well as decreased IL-4 and IL-10 levels in the lungs. SFI was associated with lower IL-6 and IL-8 concentrations and higher IL-4 and IL-10 concentrations in lung tissue. SFI attenuates HIRI through the induction of ferroptosis via JAK2/STAT3 pathway.^[30] Current findings have suggested that SFI can attenuate lung apoptosis by regulating Na⁺-K⁺-ATPase and Ca²⁺-Mg⁺-ATPase activities, respectively.

Recently, Wang et al.^[31] reported that SFI protected cardiomyocytes against apoptosis by reducing Bcl-2 and activating caspase-3. Moreover, we investigated the anti-apoptotic mechanisms of SFI and found that Bcl-2 and Bax proteins may be involved in the protective mechanisms in the lungs after HS. Therefore, SFI significantly inhibited caspase-3 expression, which decreases apoptosis in the lungs.

The present study demonstrated that SFI effectively inhibits cell apoptosis and reduces inflammatory factor levels in HS-induced lung injury, which may be mediated by multiple interconnected pathways. First, SFI regulates the balance of apoptotic regulatory proteins: downregulating caspase-3 and upregulating Bcl-2, which inhibits the mitochondrial apoptotic

pathway by preventing mitochondrial outer membrane permeabilization and cytochrome c release.^[32] Second, SFI alleviates oxidative stress, as evidenced by elevated SOD activity and reduced MDA levels, which in turn inhibits oxidative stress-induced activation of proinflammatory signaling pathways and apoptotic cascades. Third, SFI suppresses the HMGB1-NF-κB pathway, thereby inhibiting the transcription and release of proinflammatory cytokines (IL-6, IL-8) and promoting the secretion of anti-inflammatory cytokines (IL-4, IL-10) to restore the proinflammatory/anti-inflammatory balance. Additionally, SFI may attenuate apoptosis and inflammation by downregulating the MEK-ERK signaling pathway, further protecting lung tissue structure and function. These pathways synergistically contribute to the protective effects of SFI against HS-induced injury.

Accordingly, future studies are warranted to explore the synergistic effects of SFI in combination with restrictive fluid resuscitation or other standardized resuscitation protocols, which may further optimize the therapeutic strategy for HS. Although the present study focused on the efficacy of SFI as an adjuvant to blood reinfusion, our results support the potential translational value of SFI as an adjunctive therapeutic agent for clinical HS resuscitation.

Limitations

This study has several limitations. The model used healthy animals without concomitant traumatic injuries, limiting translation to polytrauma patients. Because only 23 of 32 animals survived to the 6-hour assessment, tissue-based comparisons may be affected by differential survival and survivor bias. The small and unequal numbers available for each outcome limit causal interpretation. Additionally, the absence of a sham-operated control group

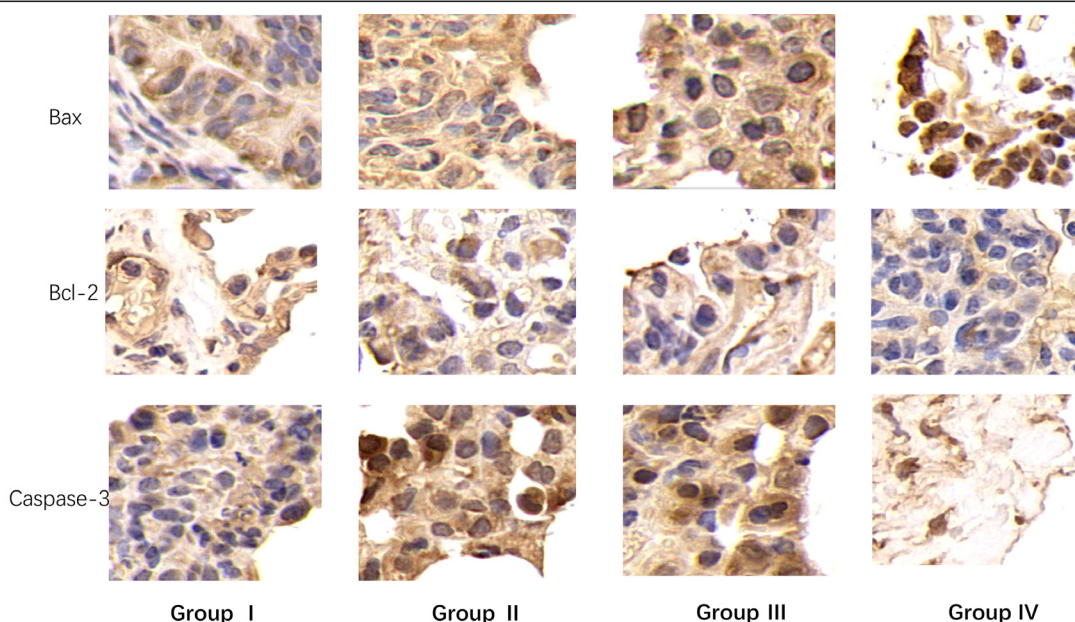


Figure 4. Bax, bcl, and caspase-3 of each group. The results showed upregulation of BCL-2; downregulation of Bax expression and caspase-3 were detected in group IV than other groups.

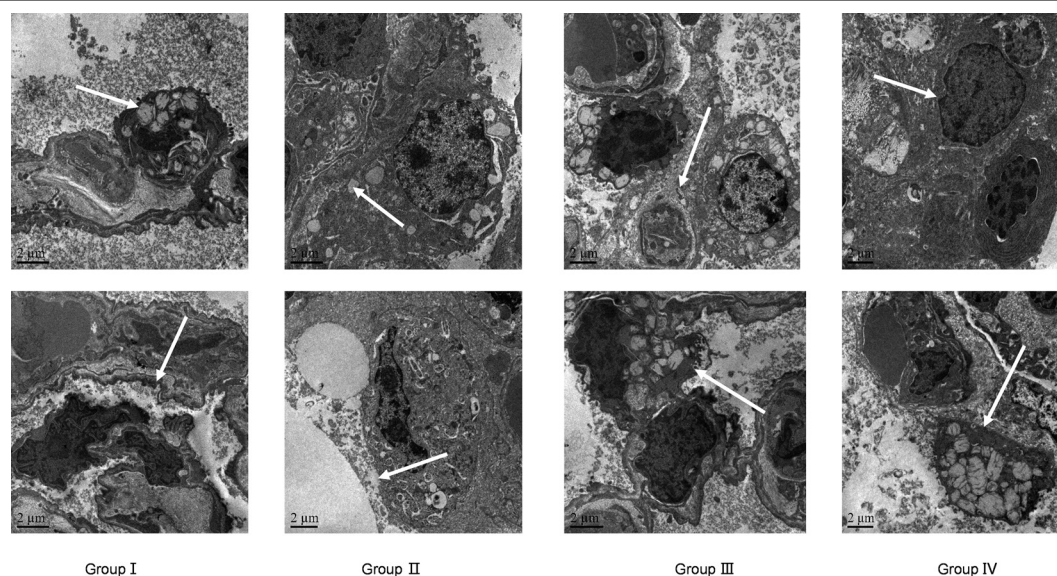


Figure 5. Ultrastructural changes of the lung at 200. Apoptosis of type II epithelial cells and mitochondrial injury of the lung of the SFI group were decreased, as shown by the arrow. SFI, Shen-fu injection.

prevents complete separation of HS-specific injury from surgical stress. Future studies should include sham controls, evaluate mitochondrial function and ATP production, and explore combinations with restrictive resuscitation protocols.

Conclusion

Among animals surviving to the 6-hour assessment, SFI was associated with differences in selected inflammatory, oxidative-stress, apoptosis, and histological markers. Because of differential mortality, small outcome-specific sample sizes, and limited quantitative histology, these findings should be considered exploratory and do not establish improved survival or hemodynamic benefit.

SFI enhanced $\text{Na}^+\text{-K}^+\text{-ATPase}$ and $\text{Ca}^{2+}\text{-ATPase}$ activities in lung tissue, which may contribute to cellular function and membrane stability, but direct effects on energy metabolism require further investigation.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Gu W designed the study. Zhang Q and Liu Z collected the data. Zhang Q and Liu B analyzed the data and wrote the

original manuscript. All authors have read and approved the final manuscript.

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Ethical approval of studies and informed consent

The animal experiments were conducted from 2023 to 2024 under protocol 2022-04-054, approved by the Animal Care and Use Committee of Capital Medical University on and valid for the study period. Any protocol renewal or amendment is identified by [2022-04-054].

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None.

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