Original Article

Effect of Shen-Fu Injection Pretreatment to Myocardial Metabolism During Untreated Ventricular Fibrillation in a Porcine Model

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Abstract

Background: Shen-Fu injection (SFI) can attenuate ischemia-reperfusion injury, protect cardiac function, and improve microcirculation during cardiopulmonary resuscitation. We hypothesized that SFI may also have an influence on myocardial metabolism during ventricular fibrillation (VF). In this study, we used SFI pretreatment prior to VF to discuss the changes of myocardial metabolism and catecholamine (CA) levels during untreated VF, trying to provide new evidence to the protection of SFI to myocardium.

Methods: Twenty-four pigs were divided into three groups: Saline group (SA group), SFI group, and SHAM operation group (SHAM group). Thirty minutes prior to the induction of VF, the SFI group received 0.24 mg/ml SFI through an intravenous injection; the SA group received an equal amount of sodium chloride solution. The interstitial fluid from the left ventricle (LV) wall was collected through the microdialysis tubes during VF. Adenosine diphosphate (ADP), adenosine triphosphate (ATP), and Na^+-K^+-ATPase and $Ca2^+$-ATPase enzyme activities were measured after untreated VF. Peak-to-trough VF amplitude and median frequency were analyzed for each of these 5-s intervals.

Results: The levels of glucose and glutamate were lower after VF in both the SA and SFI groups, compared with baseline, and the levels in the SFI group were higher than those in the SA group. Compared with baseline, the levels of lactate and the lactate/pyruvate ratio increased after VF in both SA and SFI groups, and the levels in the SFI group were lower than those in the SA group. In both the SA and SFI groups, the levels of dopamine, norepinephrine, and epinephrine increased significantly. There were no statistical differences between the two groups. The content of ATP, ADP, and phosphocreatine in the SFI group was higher than those in the SA group. The activity of LV Na^+-K^+-ATPase was significantly higher in the SFI group than in the SA group. Amplitude mean spectrum area (AMSA) was significantly lower in the SA and SFI groups at 8- and 12-min compared with 4-min. The AMSA in the SFI group was higher than that in the SA group at each time point during untreated VF.

Conclusions: SFI pretreatment can improve myocardial metabolism and reduce energy exhaustion during VF, and it does not aggravate the excessive secretion of endogenous CAs.

Key words: Cardiac Arrest; Catecholamine; Energy Metabolism; Microdialysis; Shen-Fu Injection

Introduction

Shen-Fu injection (SFI) contains ginseng (*Panax*; family: Araliaceae) and fuzi (Radix aconiti lateralis preparata, *Aconitum carmichaeli* Debx.; family: Ranunculaceae) and is a common traditional Chinese medical formulation.[1] Evidence suggests that SFI can attenuate ischemia-reperfusion injury, protect cardiac function, and improve microcirculation during cardiopulmonary resuscitation (CPR).[2] Therefore, we hypothesized that SFI may also have an influence on myocardial metabolism during ventricular fibrillation (VF).

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In the current study, we pretreated pigs with SFI before VF induction and collected myocardial interstitial fluid (ISF) using microdialysis. Changes in myocardial metabolism and catecholamine (CA) levels during untreated VF

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were examined along with amplitude mean spectrum area (AMSA) for electrocardiogram (ECG) signal analysis.

Methods

Ethics

This study was carried out in strict accordance with the guidelines for animal care and use established by the Animal Care and Use Committee of Capital Medical University. The study's experimental protocol was approved by the Committee on the Ethics of Animal Experiments of Capital Medical University (Permit Number: 2010-D-013). Animals used in this study were handled in compliance with the Guiding Principles for the Care and Use of Animals expressed in the *Declaration of Helsinki*.[3] All surgeries were performed under anesthesia and analgesia.

Preparation of experimental animals

Twenty-four Beijing Landrace pigs (males and females), aging 3–4 months and weighing 29–31 kg, were selected for this experiment. These standardized laboratory animals were provided by a registered laboratory animal center in Beijing, China. The animals had free access to drinking water, but they were fasted preoperatively overnight.

Pigs were randomly divided into three groups: Saline group (SA group), SFI group, and SHAM operation group (SHAM group) (n = 8 in each group). Thirty minutes before VF/ventricular tachycardia induction, the SFI group received 0.24 mg/ml Shen-Fu through an intravenous injection.[4] The SA group received an equal amount of sodium chloride solution (0.9%) through an intravenous injection. Fluid losses were compensated by an infusion of 30 ml/kg acetated Ringer's solution during the first hour of preparation, followed by a continuous infusion of 2.5% glucose-electrolyte solution (8 ml·kg^{-1}·h^{-1}) and acetated Ringer's solution (20 ml·kg^{-1}·h^{-1}).

The animals were anesthetized with 2 mg/kg propofol by ear vein injection. An initial dose of 30 mg·kg^{-1}·h^{-1} pentobarbital sodium was administered, followed by continuous intravenous maintenance anesthesia using 8 mg·kg^{-1}·h^{-1} pentobarbital sodium. Animals received tracheotomy, tracheal intubation, and respirator support (Drager-Evata IV, Draeger, Germany) with room air, ventilation frequency of 12 times/min, and tidal volume of 15 ml/kg. An angiographic catheter was inserted from the femoral artery into the aortic arch to measure aortic pressure. ECG and all hemodynamic parameters were monitored with a patient monitoring system (M1165; Hewlett-Packard, Palo Alto, CA, USA). A temporary pacemaker was placed into the left ventricle (LV) through a 7F trocar puncture in the left femoral vein. Room temperature was adjusted to 26°C, and body temperature was maintained at 37°C under an infrared lamp.

Experimental protocol

The chest was opened by median sternotomy, and the heart was suspended in a pericardial cradle. Heparin sodium (200 U/kg) was administered intravenously before implantation of the probe (CMA70; CMA Microdialysis AB, Kista, Sweden) to prevent blood coagulation.[5] Two microdialysis probes were separately implanted into the lateral wall of the LV myocardium midway between the apex and base of the heart, where the heart is supplied blood by the left anterior descending coronary. CMA70 catheters were perfused with Ringer's solution *in situ* for 45 min before baseline measurements were taken, and a constant flow was maintained (2.5 μl/min) using a microdialysis pump (CMA106; Microdialysis AB) [Figure 1].[6] Sinus rhythm was measured by ECG after ensuring that the pigs were stable. A medical programmable stimulator (GY-600A, Kaifeng South China Instrument Co., Henan, China) and esophageal stethoscope output (S1/S2) (300/200 ms) were used to trigger VF with continuous electrical stimulation of 10-ms steps, 8:1.[7] Diagnostic criteria for VF included a rapid drop in arterial blood pressure and ECG waveforms characteristic of VF. Ventilation was stopped while inducing VF. There was no treatment given during VF from 0 to 12 min. ECG lead II was continuously recorded with a multichannel physiological recorder (BL-420F Data Acquisition and Analysis System; Chengdu TME Technology Co., Ltd., Sichuan, China). The ISF from the LV wall was collected through the microdialysis tubes for 4-min (baseline) and collected continuously from 0 to 4, 4–8, and 8–12 min of VF. These procedures were shown in Figure 2.

After 12 min of untreated VF, the animals were sacrificed, the hearts were excised, and the right ventricles and both atria were removed. The myocardium was sampled from the anterior left ventricular wall. A part of samples were immersed in liquid N_2 within 10-s and stored at −80°C until use.[8] The remaining samples were prepared as electron microscopy specimens to observe ultrastructure tissue changes under transmission electron microscope (TEM).

Measurements

The levels of glucose, pyruvate, lactate, and glutamate were tested in the ISF, and the lactate/pyruvate (L/P) ratio was calculated. Glucose, pyruvate, and lactate levels were measured using an ISCUS flex microdialysis analyzer (CMA Microdialysis AB, Kista, Sweden). Glutamate was measured using high-performance liquid chromatography (HPLC) fluorescence assay.[9]

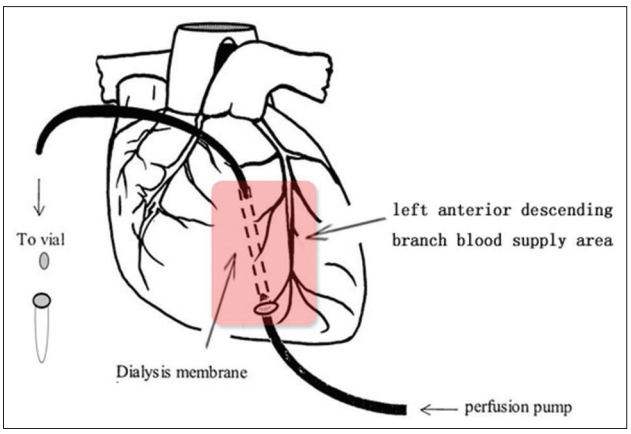

Figure 1: The probe implanted into the porcine myocardium.

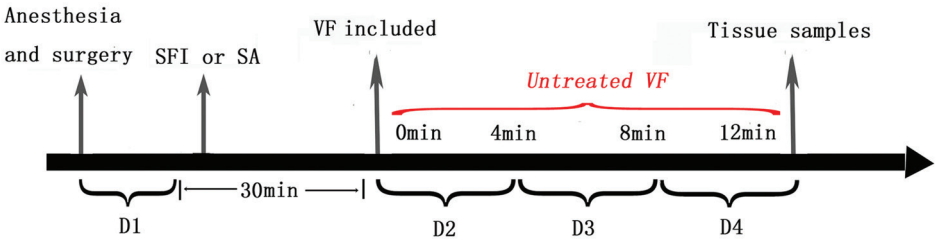

Figure 2: Flow diagram of experiment: Shen-Fu injection or saline: Shen-Fu or sodium chloride solution (0.9%) was given; VF: Ventricular fibrillation; Collect microdialysis samples: D1: Baseline (random 4-min); D2: VF 0–4 min; D3: VF 4–8 min; D4: VF 8–12 min.

Levels of dopamine, norepinephrine, and epinephrine were measured in the ISF using an HPLC fluorescence assay and a chromatographic column (2.1 mm × 100 mm, 3 μm).

Adenosine diphosphate (ADP) and adenosine triphosphate (ATP) were measured with reversed-phase HPLC (System Gold HPLC system with 32 Karat Software 5.0; Beckman Coulter, Brea, CA, USA).[10] The percentage of phosphorylated creatine was calculated relative to the combined phosphocreatine and creatine pool. Enzyme activity was assessed by measuring the optical density of inorganic phosphate decomposed from ATP by tissue protein as previously described.[11] Na^+-K^+-ATPase and Ca^{2+}-ATPase enzyme activities were determined using standard formulas.

ECG signals were sampled and recorded at 500 Hz and digitized with a data acquisition system (BL-420F Data Acquisition and Analysis System; Chengdu TME Technology Co., Ltd.). ECG signals were filtered between 4 and 50 Hz to minimize interference. Measurements were determined during representative 5-s intervals at 4-, 8-, and 12-min of untreated VF in the SA and SFI groups. Peak-to-trough VF amplitude and median frequency were analyzed for each of these 5-s intervals. AMSA of each 5-s interval was calculated with the following formula: AMSA = $\sum A_i \times F_i$, where A_i is the amplitude at i^{th} frequency F_i.[12]

Statistical analysis

All analyses were conducted using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 6 software (GraphPad Software, La Jolla, CA, USA). Normally distributed data were expressed as a mean ± standard deviation (SD). The variables from all groups were compared by repeated measures analysis of variance (ANOVA), and time point comparisons were carried out by the least significant difference. Comparisons between two groups were made with Student's *t*-test. A $P < 0.05$ was considered as statistically significant.

Results

Lactate/pyruvate ratios and glucose, glutamate, and lactate levels

Figure 3 showed that the levels of glucose and glutamate were lower after VF in both the SA and SFI groups, compared with baseline. There were no changes in the SHAM group. The levels in the SFI group were higher than those in the SA group, except at baseline (SFI vs. SA: Glucose: $t_{4\ min} = 3.01$, $P_{4\ min} = 0.011$; $t_{8\ min} = 3.14$, $P_{8\ min} = 0.008$; $t_{12\ min} = 3.11$, $P_{12\ min} = 0.009$; glutamate: $t_{4\ min} = 2.86$, $P_{4\ min} = 0.032$; $t_{8\ min} = 4.02$, $P_{8\ min} = 0.002$; $t_{12\ min} = 4.18$, $P_{12\ min} = 0.001$).

Compared with baseline, the levels of lactate and the L/P ratio increased after VF in both the SA and SFI groups. The levels in the SFI group were lower than those in the SA group, except at baseline (SFI vs. SA: Lactate: $t_{4\ min} = 4.01$, $P_{4\ min} = 0.002$; $t_{8\ min} = 4.14$, $P_{8\ min} = 0.002$; $t_{12\ min} = 2.48$, $P_{12\ min} = 0.040$; L/P ratio: $t_{4\ min} = 3.61$, $P_{4\ min} = 0.004$; $t_{8\ min} = 3.63$, $P_{8\ min} = 0.006$; $t_{12\ min} = 3.40$, $P_{12\ min} = 0.005$).

Catecholamine levels in the interstitial fluid

In both the SA and SFI groups, the levels of dopamine, norepinephrine, and epinephrine increased significantly, compared with baseline. There were no statistical differences between the two groups. The CA levels in the SHAM group did not change across time points [Table 1].

Myocardial energy metabolites at 12-min of untreated ventricular fibrillation

The content of ATP, ADP, and phosphocreatine in the SFI group was higher than those in the SA group [Table 2]. The activity of LV Na^+-K^+-ATPase was significantly higher in the SFI group than in the SA group.

Amplitude mean spectrum area analysis

AMSA was significantly lower in the SA and SFI groups at 8- and 12-min compared with 4-min [Figure 4]. The AMSA in the SFI group was higher than that in the SA group at each time point during untreated VF [Figure 5].

Myocardial histology

In the SHAM group under light microscope, the myocardial fibers were arranged neatly, and the myocardial cell morphology was normal. In the SA group, the myocardial fibers were obviously enlarged, there was myocardial cell hypertrophy, and the nuclei were large and irregularly shaped. However, only few myocardial fibers were enlarged in the SFI group [Figure 6a-6c]. Under TEM, the myocardial fibers were obviously disordered in the SA group. In addition, most of the mitochondria had vague cristae and

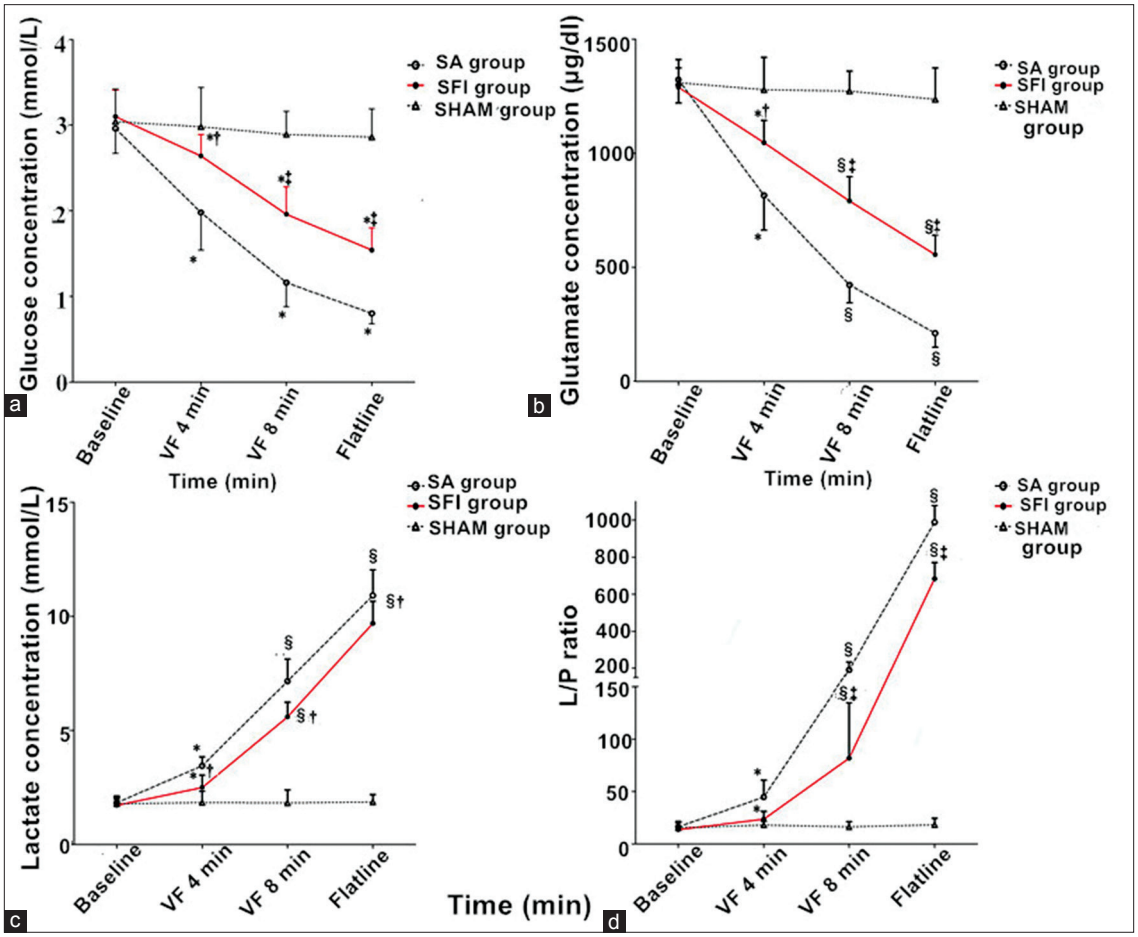

Figure 3: The levels of glucose (a), glutamate (b), lactate (c), and L/P ratio (d). Lac: Lactate; L/P: Lactate/pyruvate; SFI: Shen-Fu injection; SA: Saline. The levels of glucose and glutamate were lower after ventricular fibrillation in both the SA and SFI groups, compared with baseline. There was no change in the SHAM group. The levels in the SFI group were higher than those in the SA group, except at baseline. Compared with baseline, the levels of lactate and the L/P ratio increased after ventricular fibrillation in both the SA and SFI groups. The levels in the SFI group were lower than those in the SA group, except at baseline. Concentration levels of all from the SA and SFI groups were compared by repeated measures analysis of variance; $^{*}P < 0.05$ compared with baseline; $^{\S}P < 0.01$ compared with baseline. The Student's *t*-test was used for comparisons between two groups at equivalent time points; $^{\dagger}P < 0.05$ versus SA group; $^{\ddagger}P < 0.01$ versus SA groups.

Table 1: Comparison of DA, NE, and EP levels in the ISF during untreated VF (n = 8 in each group)

Items	SHAM group	SA group	SFI group	*t* (SFI group vs. SA group)	*P* (SFI group vs. SA group)
DA (ng/ml)					
Baseline	492 ± 70	480 ± 91	496 ± 125	0.34	0.740
At 4-min of VF	507 ± 65	2206 ± 342*	2256 ± 449*	0.36	0.730
At 8-min of VF	511 ± 46	6010 ± 499*	6200 ± 534*	0.88	0.410
At 12-min of VF	515 ± 32	7537 ± 510*	7699 ± 632*	0.64	0.540
NA (ng/ml)					
Baseline	2095 ± 279	2066 ± 307	2106 ± 374	0.39	0.700
At 4-min of VF	2102 ± 234	4145 ± 421*	4062 ± 518*	0.38	0.710
At 8-min of VF	2181 ± 267	5972 ± 286*	6033 ± 389*	0.35	0.720
At 12-min of VF	2208 ± 451	7944 ± 507*	8021 ± 623*	0.31	0.790
EP (ng/ml)					
Baseline	1258 ± 187	1171 ± 167	1232 ± 247	0.43	0.670
At 4-min of VF	1302 ± 108	2920 ± 363*	3043 ± 571*	0.51	0.620
At 8-min of VF	1324 ± 113	4493 ± 700*	4596 ± 630*	0.45	0.660
At 12-min of VF	1342 ± 107	5941 ± 450*	6127 ± 501*	0.88	0.400

Values were shown as mean ± SD. $^{*}P < 0.05$, compared with baseline. SD: Standard deviation; DA: Dopamine; NE: Norepinephrine; EP: Epinephrine; SFI: Shen-Fu injection; SA: Saline; ISF: Interstitial fluid; VF: Ventricular fibrillation.

Table 2: Myocardial energy effects of SFI at 12-min of untreated VF (n=8 in each group)

Items	SHAM group	SA group	SFI group	t (SFI group vs. SA group)	P (SFI group vs. SA group)
ATP (nmol/mg)	15.21±1.24	9.53±0.72*	11.27±1.53*†	2.91	0.006
ADP (nmol/mg)	1.74±0.57	0.54±0.28*	1.01±0.43*†	2.59	0.011
Phosphocreatine (nmol/mg)	28.46±0.51	11.92±1.75*	19.21±0.93*†	10.40	<0.001
Na^+-K^+-ATPase (U)	7.89±1.22	3.37±1.08*	5.65±0.96*†	4.46	<0.001
Ca^{2+}-ATPase (U)	8.46±1.14	3.01±0.68*	4.24±0.89*†	3.15	0.004

Values were shown as mean ± SD. SD: Standard deviation; SFI: Shen-Fu injection; ATP: Adenosine triphosphate; ADP: Adenosine diphosphate; SA: Saline; SFI: Shen-Fu injection. *P < 0.05, vs. SHAM group; †P < 0.05, vs. SA group.

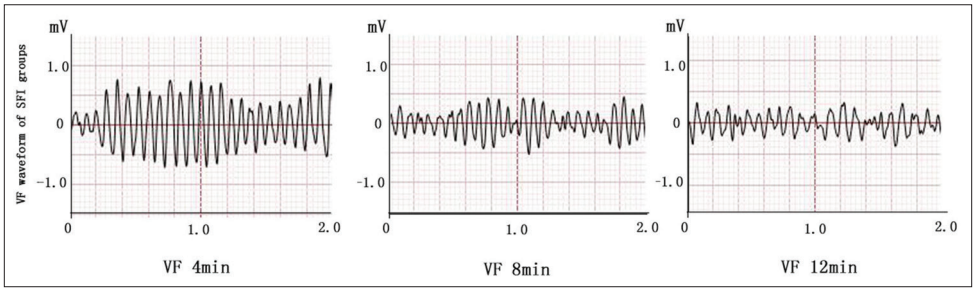

Figure 4: Changes of ventricular fibrillation waveform of Shen-Fu injection groups. VF: Ventricular fibrillation.

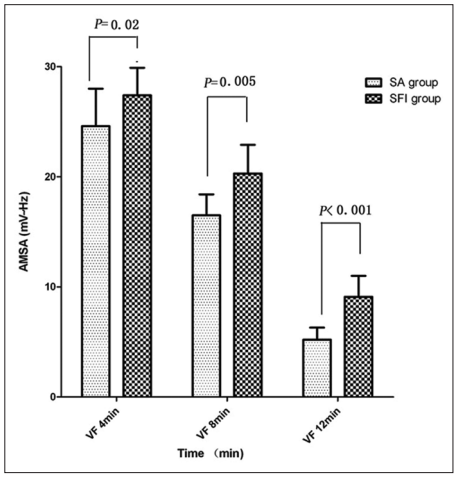

Figure 5: The amplitude spectrum area of SA and SFI groups. SFI: Shen-Fu injection; SA: Saline; AMSA: The amplitude spectrum area. The bar length represented the standard deviation.

irregular arrangements. Compared with the SA group, there were significantly fewer lesions in the SFI group, which manifested as neatly arranged myofibrils and smooth mitochondrial cristae [Figure 6d-6f].

Discussion

The effects of SFI on myocardial function have previously been studied and include dilating the coronary arteries, enhancing myocardial contractility, slowing heart rate, decreasing myocardial oxygen consumption, and improving ischemic recovery.[4,13] However, most existing research used SFI after the return of spontaneous circulation. Instead, we focused on the effects of SFI pretreatment before VF to uncover whether SFI can provide better results for CPR. In addition, previous studies mostly used plasma samples, while we collected ISF directly by microdialysis probes, which better reflects changes in myocardial metabolism during VF.

We showed that ISF glucose levels declined after VF onset. This result suggested that extracellular glucose might be taken up more rapidly during ischemia to supply energy via anaerobic glycolysis.[14] However, the glucose levels in the SFI group were higher than those in the SA group during VF, which indicates that SFI pretreatment could reduce myocardial glycogen consumption under ischemia. The SFI group also had lower lactate levels than those in the SA group, which demonstrated that SFI could reduce the production of lactate and may weaken myocardial contractility inhibition via lactate.[14]

The L/P ratio is an important indicator that reflects the relationship between aerobic oxidation and anaerobic glycolysis. During anaerobic glycolysis, pyruvate is converted to lactate.[15] In this study, the L/P ratio increased during VF, and there was a lower L/P ratio in the SFI group than in the SA group. This result suggested that SFI pretreatment might delay the transition from aerobic oxidation to anaerobic glycolysis in myocardium after VF onset, which could lead to decreased myocardial energy depletion during ischemia. Meanwhile, the levels of glutamate in the SFI group were higher than those in the SA group during VF. Glutamate can stimulate pyruvate transamination, which converts lactate into alanine via pyruvate in the ischemic myocardium and removes the inhibition of a key glycolytic enzyme caused by lactate accumulation.[16] Therefore, SFI pretreatment before VF could effectively reduce the production of metabolic waste and improve myocardial contractility.

It was reported that administering epinephrine during VF could cause myocardial tetanic contraction, which

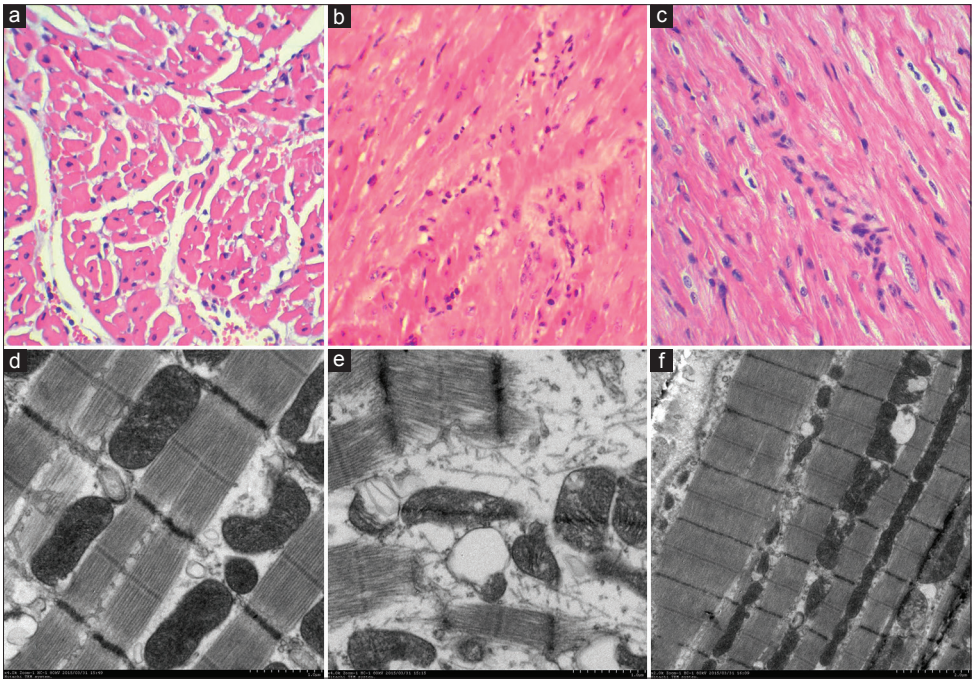

Figure 6: Myocardial tissue in the SHAM (a), saline (b), and Shen-Fu injection (c) groups under light microscope (Hematoxylin-eosin staining, original magnification ×400). Compared with the saline group, the myocardial fibers were arranged more neatly in the Shen-Fu injection group. Myocardial ultrastructure in the SHAM (d), saline (e) and Shen-Fu injection (f) groups under an electron microscope (original magnification ×30,000). The myocardial fibers were obviously disordered in the saline group. In addition, most of the mitochondria had vague cristae and irregular arrangements. Compared with the saline group, the Shen-Fu injection group manifested as neatly arranged myofibrils and smooth mitochondrial cristae.

increases oxygen consumption and irritability of the myocardium.[17] In the current study, we found that CA levels in the ISF sharply increased after VF onset, but there was no statistical difference between the SA and SFI groups. This result indicated that SFI does not influence endogenous CA secretion or sympathetic hyperactivity. Ji *et al*.[18] previously found that SFI can attenuate postresuscitation myocardial dysfunction by preventing impaired myocardial β-adrenergic receptor signaling after CPR. These results combined with ours suggest that SFI might be optimal because it can not only protect myocardial function after the return of spontaneous circulation but also protect from myocardial injury via excessive endogenous CA secretion.

The previous study identified a relationship between myocardial energy stores and VF amplitude. The decaying electrical activity of the VF ECG correlates with decaying ATP stores, which suggests that derangement of myocardial energy metabolism is a mediator of defibrillation susceptibility.[19] In addition, AMSA was shown to have a better positive predictive value for successful defibrillation than mean amplitude and median frequency of VF.[12]

We found that the activities of Na^+-K^+-ATPase and Ca^{2+}-ATPase in the SFI group were higher than those in the SA group at 12-min of untreated VF. In addition, the contents of ATP, ADP, and phosphodiesterase in the SA group were lower than those in the SFI group, which implies more energy expenditure in the SA group. Accordingly, the AMSA in the SA group was lower than that in the SFI group. It was previously reported that SFI can restore the ability of Na^+-K^+-ATPase and Ca^{2+}-ATPase enzyme activities.[20] We also found that this effect could improve the VF waveform and may increase the success rate of defibrillation.

To further investigate the effects of SFI on the heart, we observed the histology of heart tissue samples. The reduction in myocardial lesions in the SFI group was obvious under light microscope compared with the SA group, and the myocardial fibers were arranged more neatly in the SFI group. Under TEM, there were fewer pathological changes in the myocardial ultrastructure in SFI group compared with the SA group. For example, the myocardial fibers and myoseptum were less disordered, and mitochondria were less swollen in the SFI group. These pathological changes further clarified that SFI pretreatment can improve myocardial metabolism.

Despite our findings, there are some limitations of our study. Anesthesia and surgery-induced stress could potentially stimulate the release of CAs, which would affect concentration measurements. Nevertheless, the stressors were present in all groups, and while absolute values may be altered in all of the groups, the effects of anesthesia and surgery-induced stress are probably small.

In conclusion, SFI pretreatment can improve myocardial metabolism and reduce energy exhaustion during VF, and it does not aggravate the excessive secretion of endogenous CAs.

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Conflicts of interest

There are no conflicts of interest.

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