ORIGINAL ARTICLE

Effects of Shenfu Injection (参附注射液) on Cerebral Metabolism in A Porcine Model of Cardiac Arrest

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ABSTRACT **Objective**: To investigate the effects of Shenfu Injection (参附注射液, SFI) on cerebral metabolism in a porcine model of cardiac arrest (CA). **Methods**: Thirty Wuzhishan minipigs were randomly assigned to the control group (*n*=6), epinephrine group (EP group, n=12) and SFI group (*n*=12). After 8 min of untreated ventricular fibrillation (VF), pigs in the EP group or SFI group were administered with either EP (0.02 mg/kg) or SFI (1.0 mL/kg), respectively. After successful resuscitation, cerebrospinal fluid (CSF) levels of glucose, pyruvate, lactate, glutamate and glycerol were measured at 1, 6, 12 and 24 h after recover from spontaneous circulation (ROSC). In addition, neurologic deficit score (NDS) was calculated at 24 h after ROSC. Surviving pigs were killed at 24 h after ROSC, and the brain tissue was obtained for ultra-microstructure examination. **Results**: Compared with the EP group, CSF glucose and pyruvate levels were higher (all *P*<0.01), and lactate levels were lower in the SFI group (*P*<0.01). Meanwhile, CSF glutamate and glycerol levels in the SFI group were lower in comparison to the EP group (all *P*<0.05). In addition, SFI decreased NDS at 24 h after ROSC (*P*<0.01), and alleviated the histopathological damage of the brain. **Conclusions**: SFI could alleviate brain injury after CA, which may be associated with improving cerebral metabolism.

KEYWORDS Shenfu Injection, cerebral metabolism, cardiac arrest

Despite significant progress in cardiopulmonary resuscitation (CPR), brain injury after cardiac arrest (CA) is still a common cause of death. In patients who survived to intensive care unit admission but subsequently died in the hospital, brain injury was the cause of death in 68% of out-of-hospital CA and 23% of in-hospital CA.[1] Furthermore, the neurological function of surviving patients has remained poor. It is reported that approximately 40% of survivors never awake from a vegetative state, while a third of those who do wake up suffer persistent neurologic impairments.[2] Therefore, how to improve the neurological function of patients suffered from CA is always the research focus of resuscitation field.

Epinephrine (EP) has been investigated for more than a century in experimental studies of CA and is the recommended drug in the current guidelines for advanced life support of CA.[3] However, the neuroprotective effects of EP remain controversial. One study showed that early EP administration can improve neurologic function after CA.[4] In contrary, another study demonstrated that EP was associated with disturbed cerebral microcirculation after return of spontaneous circulation (ROSC).[5] Therefore, there is urgent need to find new and effective drugs to aid in cerebral resuscitation.

Shenfu Injection (参附注射液, SFI, containing ginsenoside 0.8 mg/mL and aconitine 0.1 mg/mL) is prepared from well-known Chinese herbs ginseng (*Panax*; family: *Araliaceae*) and *Radix aconiti lateralis preparata* (*Aconitum carmichaelii* Debx; family: *Ranunculaceae*). The consistency of the quality of SFI over different batches has been ensured by fingerprint technology.[6] Previous studies have confirmed that SFI has protective roles for cerebral ischemia and hypoxia damage.[7,8] Our previous work also showed that SFI could alleviate brain inflammatory responses and edema after CA.[9] However, the neuroprotective mechanisms of SFI are still not well understood. Therefore, the main purposes of this study were to

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DOI: 10.1007/s11655-016-2616-9

investigate the effects of SFI on cerebral metabolism through changes of biochemical parameters in cerebrospinal fluid (CSF) in an established porcine model of CA.

METHODS

Animal

This study was approved by the Animal Care and Use Committee of Beijing Chaoyang Hospital and conducted according to the Utstein-style guidelines.[10] All animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals by the National Institute of Health. Thirty inbred Chinese Wuzhishan minipigs (Institute of Animal Sciences, Chinese Academy of Agricultural Sciences, Beijing, China), aged 8±1 months and weighted 20±2 kg, were used in this study. Pigs were randomized into three groups: control group (*n*=6), EP group (*n*=12) and SFI group (*n*=12).

Animal Preparation

Pigs were fasted overnight with free access to water. Initial sedation was induced by intramuscular injection of ketamine (0.5 mg/kg), followed by intravenous injection of propofol (1 mg/kg). Then propofol 9 mg/(kg•h) and fentanyl 1 μg/(kg•h) were administered intravenously to maintain the anesthesia and analgesia. A cuffed 6.5-mm endotracheal tube was advanced into the trachea of each anesthetized pig. Pigs were mechanically ventilated with a volume-controlled ventilator (Servo 900c, Siemens, Berlin, Germany) with a tidal volume of 8 mL/kg, a constant fraction of inspired oxygen (FiO_2) of 0.21, and an inspiration/expiration ratio of 1:2 with a positive end-expiratory pressure of 5 cm H_2O. End-tidal $PaCO_2$ ($PetCO_2$) was monitored with an in-line infrared capnograph system (CO_2SMO Plus monitor, Respironics Inc., Murrysville, Pennsylvania, USA). The respiratory frequency was adjusted to maintain $PetCO_2$ between 35–40 mm Hg.

The right femoral artery and femoral vein were exposed, followed by the right external and internal jugular vein. A 6-Fr catheter was advanced from the right femoral artery into the thoracic aorta to measure aortic pressure. A Swan-Ganz catheter (7F, Edwards Life Sciences, Irvine, California, USA) was advanced from the right femoral vein and flow-directed into the pulmonary artery to measure right atrial pressure and cardiac output (CO). A 5-Fr pacing catheter was advanced from the right external jugular vein into the right ventricle to induce ventricle fibrillation (VF). A catheter was inserted retrograde into the right internal jugular vein for blood collection. All catheters were calibrated before use. The electrocardiograph and all hemodynamic parameters were monitored by a multifunction monitor (M1165, Hewlett-Packard Company, Palo Alto, California, USA). An epidural catheter was inserted into the lumbar spine at the 3rd to 4th interval for CSF sampling and intracranial pressure (ICP) monitoring.

Experimental Protocol

After surgery, pigs were allowed to achieve a stable resting level, and baseline data were recorded. Before the VF model was established, mechanical ventilation was ceased. VF was induced by a programmed electrical stimulation instrument (GY-600A, Kaifeng Huanan Instrument Company, Kaifeng, Henan, China) with model S1/S2 (300/200 ms), 40 V, 8:1 proportion, and -10 millisecond step length, and confirmed by the presence of a characteristic electrocardiographic waveform. After 8 min of untreated VF, mechanical ventilation was resumed with 100% oxygen, and chest compression was performed manually by two designated cardiopulmonary resuscitation (CPR) technicians at a rate of 100 compressions per minute. The quality of chest compression was controlled by a HeartStart MRx Monitor/Defibrillator with Q-CPR (Philips Medical Systems, Best, Holland). After 2 min of chest compression, pigs were administered with central venous injection of either EP (0.02 mg/kg) or SFI (1.0 mL/kg), respectively. If the spontaneous circulation was not restored, defibrillation (Smart Biphasic, Holland) was attempted using 150 J for the first attempt, followed by another 2 min of chest compression. If the first defibrillation attempt was unsuccessful, 200 J was used for the second and all subsequent attempts. The sequence continued until ROSC or for 30 min if ROSC was not achieved. ROSC was defined as the maintenance of systolic blood pressure >50 mm Hg for at least 10 min. Pigs with no ROSC after 30 min of CPR were pronounced dead. For pigs in the control group, anesthesia and surgery procedures were administered without the establishment of VF model.

After 24 h of post-resuscitation monitoring, all catheters were removed by surgical procedure. The

surviving pigs were sacrificed with an over dosage of 60 mg propofol intravenous injection and then 10 mL 10% potassium chloride intravenous injection.

Measurements

Hemodynamic data were continuously recorded. ICP was measured continually, and cerebral perfusion pressure (CPP) was calculated as mean aortic pressure (MAP) minus ICP.

Internal jugular venous samples for blood gas analysis at baseline, 1, 6, 12 and 24 h after ROSC were collected and measured by blood gas analyzer (GEM Premier 3000 blood gas analyzer; Instrumentation Laboratory, Lexington, MA, USA). Lactate clearance was calculated by the formula [(initial lactate – delayed lactate)/initial lactate)] × 100%, in which initial lactate was the measurement at ROSC and delayed lactate was that at 1, 6, 12 or 24 h after ROSC.

CSF samples at baseline, 1, 6, 12 and 24 h after ROSC were collected through the epidural catheter, and CSF levels of glucose, pyruvate, lactate, glycerol and glutamate were measured with Hitachi 7170A biochemistry analyzer (Hitachi, Ibaraki, Japan).

Neurological function was evaluated with the porcine quantitative neurological deficit score (NDS), which includes consciousness level, breathing pattern, function of cranial nerve, function of sensory and motor nerve. In our study, NDS was evaluated at 24 h after ROSC, and agreed on by two experienced researchers on the basis of double blindness.

Brain tissue was preserved in 10% formaldehyde and 4% paraformaldehyde. The ultra-microstructure of brain tissue was observed using light microscopy and TEM (H-7650; Hitachi, Ibaraki, Japan).

Statistical analysis

All data were analyzed using Statistical Package for the Social Sciences (SPSS) 17.0 statistics software (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation ($\bar{x} \pm s$) for continuous variables and as percentages for categorical data. Comparisons of continuous variables among groups at selected time points were performed with one-way ANOVA, and Bonferroni's test was used for post hoc comparisons. A two-tailed *P* value <0.05 was considered statistically significant.

RESULTS

Resuscitation Outcome

Twenty-one pigs were successfully resuscitated, 10 in the EP group and 11 in the SFI group. There were no significant differences in the rate of ROSC between the two groups ($P>0.05$). In addition, differences in survival rate at 1, 6, 12 and 24 h after ROSC were not significant between the two groups (all $P>0.05$; Table 1).

Table 1. Resuscitation Outcomes in the Pigs

Group	Time	Survival [n (%)]
EP (*n*=12)	Baseline	10 (83.3)
	ROSC 1 h	10 (83.3)
	6 h	8 (66.7)
	12 h	8 (66.7)
	24 h	6 (50.0)
SFI (*n*=12)	Baseline	11 (91.7)
	ROSC 1 h	11 (91.7)
	6 h	10 (83.3)
	12 h	9 (75.0)
	24 h	8 (66.7)

Data of Cerebral Perfusion

MAP was significantly higher in the SFI group compared with the EP group at 6 h after ROSC. However, there were no significant differences in MAP between the two groups at 1, 12 and 24 h after ROSC. ICP in the EP and SFI groups increased at 1, 6 and 12 h after ROSC, and declined to baseline levels at 24 h after ROSC. The ICP in the SFI group was significantly lower than that in the EP group at 1, 6 and 12 h after ROSC. Compared with the control group, CPP in the EP group declined significantly at 1, 6 and 12 h after ROSC, and in the SFI group at 6 and 12 h after ROSC. On the other hand, CPP in the SFI group at 1, 6 and 12 h after ROSC was significantly higher than the EP group (Table 2).

Results of Jugular Venous Blood Gas Analysis

The initial jugular venous lactate levels were similar among the three groups. Jugular venous lactate levels in EP and SFI groups increased significantly at 1, 6 and 12 h after ROSC and returned to baseline levels at 24 h after ROSC. In addition, jugular venous lactate levels in the SFI group were lower than in the EP group at 1, 6 and 12 h after ROSC. Compared with the EP group, lactate

Table 2. Data of Cerebral Perfusion in the Pigs (mm Hg, $\bar{x} \pm s$)

Group	Time	MAP	ICP	CPP
Control	Baseline	109.7±3.7	9.3±1.0	100.2±4.3
	ROSC 1 h	107.8±3.8	9.3±0.8	99.1±3.7
	6 h	111.3±2.3	9.5±1.1	102.2±4.7
	12 h	111.5±3.2	10.0±1.3	101.4±5.1
	24 h	109.7±3.7	10.0±1.1	99.2±4.9
EP	Baseline	109.6±3.6	9.8±1.1	100.2±3.9
	ROSC 1 h	109.2±4.9	15.0±1.2**	94.4±4.8*
	6 h	106.6±3.1	18.1±1.5**	88.1±5.7**
	12 h	110.3±4.5	18.9±2.0**	92.2±6.7**
	24 h	110.7±2.9	12.0±1.8	98.4±3.9
SFI	Baseline	108.9±4.7	10.3±1.2	99.3±3.6
	ROSC 1 h	111.8±3.6	13.5±1.4**△	98.1±4.9△
	6 h	111.4±4.5△	15.9±1.4**△△	96.2±5.4*△△
	12 h	111.0±3.5	16.8±1.4**△	95.3±5.9*△
	24 h	110.1±3.9	10.9±1.6	99.3±4.6

Notes: *P<0.05, **P<0.01 *vs*. control group; △P<0.05, △△P<0.01 *vs*. EP group

clearance in the SFI group was significantly higher at 1, 6, and 12 h after ROSC. Saturation of jugular venous oxygen ($SJVO_2$) in the SFI group decreased at 1, 6 and 12 h and then increased to baseline at 24 h after ROSC. Moreover, $SJVO_2$ in the SFI group were significantly lower than the EP group at 1, 6 and 12 h after ROSC (Table 3).

Table 3. Results of Jugular Venous Blood Gas Analysis ($\bar{x} \pm s$)

Group	Time	Lactate (mmol/L)	LC (%)	$SJVO_2$ (%)
Control	Baseline	1.8±0.2	–	64.7±3.5
	ROSC 1 h	1.8±0.1	–	65.3±1.9
	6 h	1.8±0.1	–	65.2±2.3
	12 h	1.8±0.1	–	65.8±2.0
	24 h	1.8±0.2	–	65.3±1.8
EP	Baseline	1.9±0.1	–	64.1±2.9
	ROSC 1 h	10.5±0.5*	21.8±5.3	66.3±2.6
	6 h	8.2±0.3*	45.9±6.2	65.4±3.3
	12 h	4.2±0.3*	65.5±6.8	66.3±2.8
	24 h	2.0±0.1	82.6±5.5	62.7±2.3
SFI	Baseline	1.8±0.1	–	64.3±3.9
	ROSC 1 h	8.5±0.3*△	48.2±7.6△	62.6±2.8△
	6 h	5.9±0.2*△	74.2±7.0△	55.6±3.0*△
	12 h	3.4±0.1*△	82.9±7.7△	54.2±3.0*△
	24 h	1.9±0.1	84.5±6.3	62.5±2.2

Notes: *P<0.01 *vs*. control group; △P<0.01 *vs*. EP group

CSF Levels of Biochemical Parameters

Glucose levels in the EP and SFI groups declined in comparison to the control group at 1, 6 and 12 h after ROSC. Furthermore, glucose levels in the SFI group were significantly higher than the EP group at 6 and 12 h after ROSC (Figure 1A). Compared with the control group, pyruvate levels were significantly decreased in the EP and SFI groups at 1, 6 and 12 h after ROSC. Furthermore, pyruvate levels were significantly higher in the SFI group than the EP group at 6 and 12 h after ROSC (Figure 1B). Lactate significantly increased in EP and SFI groups after ROSC, which lasted until 24 h after ROSC and peaked at 1 h after ROSC. Lactate levels in the SFI group were significantly lower than the EP group at 1 and 6 h after ROSC (Figure 1C). In the EP and SFI groups, glutamate levels increased through the experiment and peaked at 12 h after ROSC. However, glutamate levels in the SFI group were all significantly lower than EP group at four time points after ROSC (Figure 1D). Glycerol levels in the EP and SFI groups were increased at 1, 6, 12 and 24 h after ROSC compared with the control group. In addition, glycerol levels in the SFI group were significantly lower than in EP group at 6 and 12 h after ROSC (Figure 1E).

NDS and Brain Ultra-Microstructure at 24 h after ROSC

At 24 h after ROSC the median NDS in the SFI group was significantly lower than the EP group (P<0.05; Figure 2). Ultra-microstructural changes were observed by electron microscopy. Compared with the control group (Figure 3A), the EP group showed serious brain damage, including loss of normal neuronal form, presence of nuclear deformation and solid shrinkage, mitochondrial swelling, ridge fracture, and cavity changes (Figure 3B). In addition, the SFI group exhibited less intracellular damage (Figure 3C).

DISCUSSION

SFI is the typical form of Shenfu Decoction (参附汤) for intravenous medication. In clinical practice SFI has been used for treatment of many diseases, especially being famous for its traditional cardiovascular protective effects, such as stabilizing blood pressure and improving heart function.[11,12] Moreover, some studies have proved that SFI has significant protective effects against ischemia-reperfusion injury.[13,14] Furthermore, SFI has been proven to reduce organ dysfunction after CA/CPR. For example, Ji, et al[15] confirmed that SFI

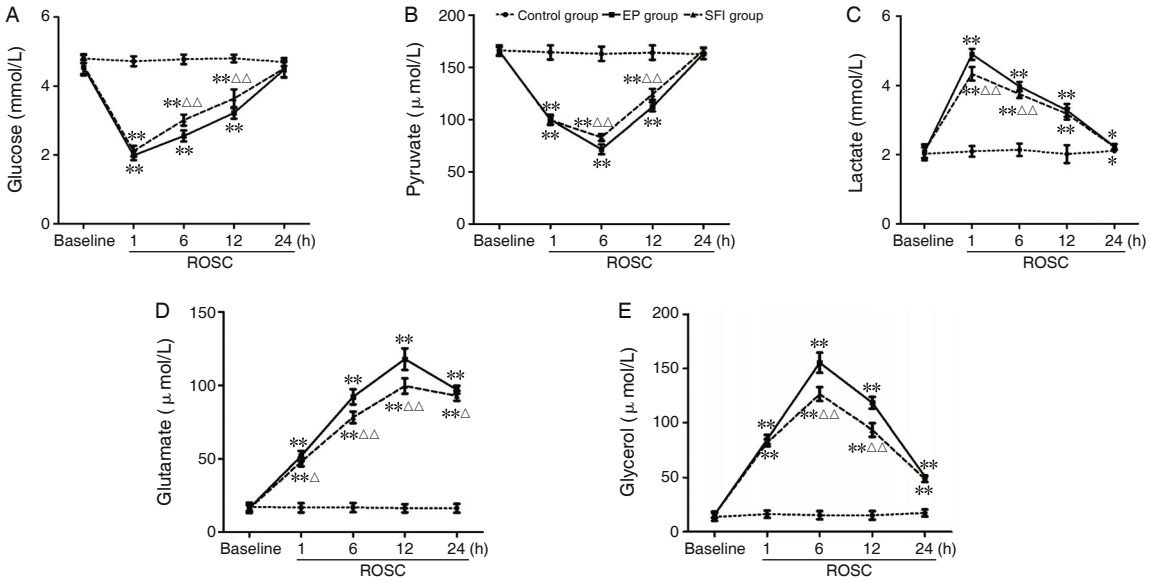

Figure 1. Cerebrospinal Fluid Levels of Biochemical Parameters

Notes: $^{*}P<0.05$, $^{**}P<0.01$ *vs*. control group; $^{\triangle}P<0.05$, $^{\triangle\triangle}P<0.01$ *vs*. EP group

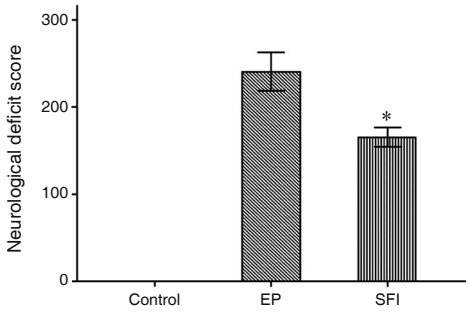

Figure 2. Neurological Deficit Score in Pigs at 24 h after ROSC

Note: $^{*}P<0.01$ *vs*. EP group

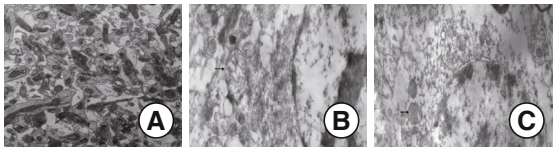

Figure 3. Brain Ultra-Microstructure of the Cortex Tissue by Electron Microscopy (×10000)

Notes: A, Normal brain ultra-microstructure in the control group; B, mitochondrial swelling was observed in the EP group (Arrow); C, mitochondrial damage was alleviated in the SFI group (Arrow)

attenuated post-resuscitation myocardial dysfunction through beneficial effects on energy metabolism and remarkable antioxidant capacity. Similarly, another study found that SFI attenuated post-resuscitation lung injury by inhibiting lung cell apoptosis, and by improving energy metabolism and antioxidant capacity.[16] Taken together, these results suggest the potential of SFI as an effective drug in the treatment of organ dysfunction after CA.

CA results in whole-body ischemia-reperfusion and represents the most severe shock state. The unique vulnerability of the brain is attributed to its limited tolerance of ischemia and unique response to reperfusion. Metabolism failure is an important mechanism of brain damage after CA, which is associated with abruptly halted delivery of oxygen and metabolic substrate, and characterized by significantly enhanced anaerobic metabolism and depressed aerobic metabolism.[17] Extracellular glucose, pyruvate and lactate are widely used parameters to reflect the metabolic status in the brain. Glucose is the only metabolic substrate of brain; the changes of glucose level can directly reflect the cerebral ischemia and hypoxia. Lactate is the end product of anaerobic metabolism, while pyruvate is the intermediate product between aerobic metabolism and anaerobic metabolism, so the ratio between lactate and pyruvate is a sensitive marker of redox state in the brain.[18] In this study, CSF levels of glucose, pyruvate and lactate were measured at four time points after ROSC. The results showed that the CSF glucose levels decreased significantly, and lactate levels increased significantly in the EP group early after ROSC, confirming the metabolic failure after severe global ischemia induced by VF. On the other hand, we found that SFI administration resulted in increased glucose levels, and decreased lactated levels after ROSC compared with the EP group. As previously stated, SFI can alleviate post-resuscitation myocardial dysfunction and lung injury by improving the energy metabolism.[15,16,19] Our results also supported that SFI can alleviate post-CA brain damage through improving

cerebral metabolism.

Noticeably, lower $SJVO_2$ in the SFI group in comparison to EP group at 1, 6 and 12 h after ROSC was observed in the present study. $SJVO_2$ can indirectly reflect the cerebral oxygen extraction, and decreased $SJVO_2$ is associated with improvement of cerebral metabolism and neurological outcome in post-CA patients.[20] Taking into account the CSF levels of glucose and lactate in the present study, one possibility could be that a switch from anaerobic glycolysis to oxidative phosphorylation which consumes more oxygen and less glucose, and produces less lactate. Taken together, these results further confirmed the beneficial effects of SFI on cerebral metabolism.

Excitotoxicity induced by release of large mount of excitatory amino acids is a proposed mechanism of brain injury after CA. Glutamate is one kind of excitatory amino acids. After CA cerebral glutamate levels may increase significantly and exerted detrimental effects to neuronal function. Multiple factors, including cellular leakage, altered synaptic transmission and inhibited reuptake, may contribute to the increase of glutamate levels after CA.[21] Among these, metabolism failure may directly contribute to the increase of glutamate levels.[22,23] In our study CSF glutamate levels increased significantly after ROSC. Furthermore, SFI significantly decreased the glutamate levels in comparison to the EP group. As previously stated, SFI can enhance the aerobic metabolism, so as to improve the function of glutamate reuptake system and decrease CSF glutamate levels.

Glycerol is the end product of degradation of cell membrane phospholipids. Under stress state, such as ischemia or hypoxia, the cell membrane is damaged and the glycerol is released. Therefore extracellular glycerol is a useful marker of the degree of cell damage.[24] Failure of cellular metabolism results in disruption of cell membrane function and ultimately leads to the increase of glycerol levels.[25] Noticeably, we observed that SFI significantly inhibited the glycerol increase normally associated with CA during the phase of ROSC. Furthermore the benefits of SFI on cerebral metabolism may also help to decrease the extent of membrane degradation.

Other prominent findings of this study were that SFI inhibited internal jugular venous lactate levels to abruptly increase and enhanced lactate clearance after ROSC. Lactate represents a technically simple parameter to assess tissue oxygen delivery and indirectly indicates tissue perfusion. Lower lactate levels indicate improved tissue perfusion and are associated with decreased mortality in post-CA patients.[26] On the other hand, the present study showed that ICP was elevated and CPP was decreased within 12 h after ROSC, and SFI depressed ICP elevation after ROSC, resulting in ameliorated CPP decrease. Meanwhile, a better neurological outcome was confirmed by less NDS and alleviated histopathological damage. These results all support that the neuroprotective effects of SFI after CA.

Several limitations of this study should be noted. First, apparently healthy pigs were used in this experiment, whereas most individuals suffering from CA have underlying diseases. Second, the potential effects of anaesthetic agents on cerebral metabolism were not assessed.

The current study investigated the effects of SFI on cerebral metabolism following CA and CPR. The key findings were as follows: (1) SFI improved cerebral metabolism, meanwhile alleviated neurotoxicity and decreased membrane degradation; (2) SFI enhanced cerebral perfusion; and (3) SFI improved neurological function after experimental CA.

Conflict of Interests

The authors declare that they have no conflicts of interest and no financial relationships to disclose.

Author Contributions

Li CS conceived and designed the study. Yin Q, Wu CJ, Yang J and Hang CC conducted the experiment. Yin Q analyzed the data and wrote the manuscript.

Acknowledgement

The authors would like to thank Drs. GUO Zhi-jun and ZHANG Yi from Emergency Department, Beijing Chaoyang Hospital, Capital Medical University for their technical assistance.

REFERENCES

1. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med 2004;30:2126-2128.
2. Longstreth WT Jr, Inui TS, Cobb LA, Copass MK. Neurologic recovery after out-of hospital cardiac arrest. Ann Intern Med 1983;98:588-592.

3. Neumar RW, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, et al. Part 8: Adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:729-S767.
4. Zuercher M, Kern KB, Indik JH, Loedl M. Hilwig RW, Ummenhofer W, et al. Epinephrine improves 24-hour survival in a swine model of prolonged ventricular fibrillation demonstrating that early intraosseous is superior to delayed intravenous administration. Anesth Analg 2011;112:884-890.
5. Ristagno G, Sun S, Tang W, Castillo C, Weil MH. Effects of epinephrine and vasopressin on cerebral microcirculatory flows during and after cardiopulmonary resuscitation. Crit Care Med 2007;35:2145-2149.
6. Tian DL, Li K, Jiang JJ, Zhu YN. Risk control system construction of Shenfu injection. China J Chin Mater Med (Chin) 2012;37:2814-2817.
7. Wang ZF, Zhong L, Li YS. The protective effects of Shenfu injection on the global cerebral ischemia/ reperfusion injury of rats. Chin J Appl Physiol (Chin) 2012;28:462-465.
8. Yang LJ, Wang J, Tian ZF, Yuan YF. Shenfu injection attenuates neonatal hypoxic-ischemic brain damage in rats. Neurol Sci 2013;34:1571-1574.
9. Hou X, Li C, Gu W, Guo Z, Yin W, Zhang D. Effect of Shenfu injection on inflammatory cytokine release and brain edema after prolonged cardiac arrest in the swine. Am J Emerg Med 2013;31:1159-1164.
10. Idris AH, Becker LB, Ornato JP, Hedges JR, Bircher NG, Chandra NC, et al. Utstein-style guidelines for uniform reporting of laboratory CPR research: a statement for healthcare professionals from a task force of the American Heart Association, the American College of Emergency Physicians, the American College of Cardiology, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Institute of Critical Care Medicine, the Safar Center for Resuscitation Research, and the Society for Academic Emergency Medicine Writing Group. Circulation 1996;94:2324-2336.
11. Li ZE. Clinical research on effects of Shenfu injection in different dosage in preventing heart failure occurred in patients of acute myocardial infarction with elevated ST segment. Chin J Integr Tradit West Med (Chin) 2006;26:555-557.
12. Hu YH, Wu HQ, Qi X. Influence of Shen-Fu injection on heart function and bone marrow stem cell mobilization in patients with chronic heart failure of coronary heart disease. Chin J Integr Tradit West Med (Chin) 2009;29:309-312.
13. Zheng SY, Sun J, Zhao X, Xu JG. Protective effect of SFI on myocardial ischemia-reperfusion injury in rats. Am J Chin Med 2004;32:209-220.
14. Zheng CD, Min S. Cardioprotection of Shenfu Injection against myocardial ischemia-reperfusion injury in open heart surgery. Chin J Integr Med 2008;14:10-16.
15. Ji XF, Yang L, Zhang MY, Li CS, Wang S, Cong LH. Shen-Fu Injection attenuates postresuscitation myocardial dysfunction in a porcine model of cardiac arrest. Shock 2011;35:530-536.
16. Zhang MY, Ji XF, Wang S, Li CS. Shen-Fu Injection attenuates postresuscitation lung injury in a porcine model of cardiac arrest. Resuscitation 2012;83:1152-1158.
17. Bahlmann L, Klaus S, Baumeier W, Schmucker P, Raedler C, Schmittinger CA, et al. Brain metabolism during cardiopulmonary resuscitation assessed with microdialysis. Resuscitation 2003;59:255-260.
18. Tisdall MM, Smith M. Cerebral microdialysis-research technique or clinical tool. Bri J Anaesthesia 2006;97:18-25.
19. Guo ZJ, Wu CJ, Li CS. Shen-Fu Injection alleviates post-resuscitation myocandial dysfunction by up-regulating expression of Sarcoplasmic reticulum Ca^{2+}-ATPase. Chin J Integr Med 2016;22:503-509.
20. Buunk G, van der Hoeven JG, Meinders AE. Prognostic significance of the difference between mixed venous and jugular bulb oxygen saturation in comatose patients resuscitated from a cardiac arrest. Resuscitation 1999;41:257-262.
21. Hillered L, Vespa PM, Hovda DA. Translational neurochemical research in acute human brain injury: the current status and potential future for cerebral microdialysis. J Neurotrauma 2005;22:3-41.
22. Takata K, Takeda Y, Sato T, Nakatsuka H, Yokoyama M, Morita K. Effects of hypothermia for a short period on histologic outcome and extracellular glutamate concentration during and after cardiac arrest in rats. Crit Care Med 2005;33:1340-1345.
23. Samuelsson C, Hillered L, Zetterling M, Enblad P, Hesselager G, Ryttlefors M, et al. Cerebral glutamine and glutamate levels in relation to compromised energy metabolism—a microdialysis study in subarachnoid hemorrhage patients. J Cerebral Blood Flow Metab 2007;27:1309-1317.
24. Frykholm P, Hillered L, Langstrom B, Persson L, Valtysson J, Watanabe Y, et al. Increase of interstitial glycerol reflects the degree of ischaemic brain damage—a PET and microdialysis study in a middle cerebral artery occlusion reperfusion primate model. J Neurol Neurosurg Psychiatry 2001;71:455-461.
25. Reinstrup P, Stahl N, Mellergard P, Uski T, Ungerstedt U, Nordstrom CH. Intracerebral microdialysis in clinical practice: baseline values for chemical markers during wakefulness, anesthesia, and neurosurgery. Neurosurgery 2000;47:701-709.
26. Donnino MW, Miller J, Goyal N, Loomba M, Sankey SS, Dolcourt B, et al. Effective lactate clearance is associated with improved outcome in post-cardiac arrest patients. Resuscitation 2007;75:229-234.

(Received July 20, 2015)
Edited by GUO Yan