ORIGINAL ARTICLE

Comparison of Shenfu Injection (参附注射液) and Epinephrine on Catecholamine Levels in A Porcine Model of Prolonged Cardiac Arrest*

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ABSTRACT   **Objective:** To compare the effects of Shenfu Injection (SFI) and epinephrine (EPI) on catecholamine levels in a porcine model of prolonged cardiac arrest (CA). **Methods:** After 8 min of untreated ventricular fibrillation, 24 Wuzhishan miniature pigs were randomly assigned to one of the three groups (n=8 per group) and received central venous injection, respectively: SFI group (1 mL/kg), EPI group (20 μg/kg EPI), and normal saline (NS) group. Cardiac output (CO), maximum rate of increase/decrease in left ventricular pressure (±dp/dt), serum levels of EPI, norepinephrine (NE), and dopamine (DA) were determined at baseline and at 0.5, 1, 2, and 4 h after restoration of spontaneous circulation. **Results:** The duration of cardiopulmonary resuscitation was shorter in the EPI and SFI groups than in the NS group (P<0.05). The EPI level increased significantly after restoration of spontaneous circulation (ROSC) in all three groups, and was significantly different between the EPI group and the other two groups immediately after ROSC (both P<0.01), but these differences gradually disappeared over time. There were no significant differences in NE or DA levels among the three groups, and there were no correlations between catecholamine levels and CO or dp/dt (P>0.05). **Conclusions:** SFI did not significantly affect endogenous catecholamine levels during cardiopulmonary resuscitation after prolonged ventricular fibrillation. However, SFI improved oxygen metabolism, and produced a better hemodynamic status compared with EPI. SFI might be a potentially vasopressor drug for the treatment of CA.
KEYWORDS   cardiac arrest, ventricular fibrillation, cardiopulmonary resuscitation, catecholamine, Shenfu Injection

Cardiac arrest (CA) is one of the leading causes of death.[1] Sudden death due to CA results in about 400,000 deaths every year in the United States.[2] During the process of CA, high-quality cardiopulmonary resuscitation (CPR) and rapid defibrillation are of primary importance and drug administration is of secondary importance.[3] A vasopressor agent might improve coronary and cerebral blood flow and thereby facilitates resuscitation after CA. Epinephrine (EPI) has been used as a first-choice vasopressor drug for the treatment of human CA since 1974.[4] However, the administration of EPI is controversial. A randomized, double-blind, placebo-controlled trial reported that the administration of EPI during CA did not result in a significant improvement in the survival rate of patients discharged from the hospital.[5] Another clinical study reported that administration of EPI was significantly correlated to decreased chances of survival and good functional outcomes.[6] Researchers have searched extensively for optimal vasopressor agent. Unfortunately, no placebo-controlled trials have shown that administration of any vasopressor agent at any

stage during treatment of ventricular fibrillation (VF) increased the rate of neurologically intact survival of patients after hospital discharge.

Shenfu Injection (参附注射液, SFI) is an extract of traditional Chinese herbs. Our previous study showed that SFI can attenuate post-resuscitation myocardial dysfunction and improve energy metabolism and antioxidant capacity.[7] We also found that SFI can significantly improve cardiogenic shock haemodynamics and oxygen metabolism in dogs.[8] However, the effects of SFI on restoration of spontaneous circulation (ROSC) remain unknown. We

therefore designed this study to determine whether SFI facilitates resuscitation and analyze the correlation between the outcome and serum catecholamine levels.

METHODS

Animals

This study was approved by the Animal Care and Use Committee of Chaoyang Hospital of Capital Medical University, China. Twenty-four inbred Wuzhishan miniature pigs (aged 12–14 months, weight 30 ± 2 kg) were used (animal license No. Beijing 2008-050109, provided by Chinese Academy of Agricultural). All of the animals were maintained in a pathogen-free environment in our facility, and were fed standard chow. All animal experiments were performed in a humane manner, and in accordance with the Institutional Animal Care Instructions. The experimental protocol was approved by the Animal Experimentation Ethics Committee of Capital Medical University, China (Permit No. 2010-D-013).

Drugs Preparation

SFI was provided by Ya'an Sanjiu Pharmaceutical Co., Ltd. (No. 110804, Ya'an, China), which is composed of *Panax ginseng* C. A. Mey and *Radix Aconitum Carmichaeli*. The main components of SFI include ginsenoside (0.8 mg/mL) and aconitine (0.1 mg/mL). SFI was prepared as working procedure which was showed in our previous study.[9]

Main Instruments

The main instruments used were as follows: volume-controlled ventilator (Servo 900C, Siemens, Munich, Germany), infrared monitor (CO_2SMO Plus monitor, Respirometric Inc, Murrysville, PA, USA), Swan-Ganz catheter (7-Fr, Edwards Life Sciences, CA, USA), Cardiac output (CO) monitor (Vigilance Ⅱ, Edwards Life Sciences, USA), BL-420F data acquisition & analysis system (Chengdu TME Technology Co. Ltd., Sichuan, China), electrical stimulator (GY-600A, Kaifeng Huanan Equipment Co., Ltd, Kaifeng, China), heartstart MRx monitor/defibrillator with Q-CPR (Philips Medical Systems, Best, The Netherlands), GEM Premier 3000 blood gas analyzer (Instrumentation Laboratory, Lexington, MA, USA).

Animal Preparation

The animals were fasted overnight with free access to water. After premedication with intramuscular ketamine (10 mg/kg), anesthesia was induced by ear vein injection of propofol (1.0 mg/kg) and was maintained by intravenous infusion of 8 mg/(kg·h) pentobarbital. The trachea was intubated with a cuffed 6.5-mm endotracheal tube. Then, the animals were mechanically ventilated with a volume-controlled ventilator using ambient air, with a tidal volume of 15 mL/kg and a frequency of 12 breath/min.

End-tidal PCO_2 was measured using an infrared monitor. Ventilatory frequency was adjusted to maintain end-tidal PCO_2 between 35 and 40 mm Hg before inducing CA. Room temperature was maintained at 26 ℃, and body temperature was maintained at 37 ℃ under an infrared lamp. Aortic pressure was measured using a fluid-filled catheter that was advanced from the left femoral artery into the thoracic aorta. Right atrial pressure was measured using a Swan-Ganz catheter that was advanced from the left femoral vein and flow-directed into the pulmonary artery. CO was measured using a CO monitor.

To induce VF, a 5-Fr pacing catheter was advanced from the right internal jugular vein into the right ventricle. Left ventricular function was measured using a fluid-filled polyurethane catheter that was introduced via the right carotid artery into the left ventricle, to determine the maximum rate of increase in left ventricular pressure (+dp/dt) and maximum rate of decrease in left ventricular pressure (–dp/dt).

Establishment of Programmed Electrical Stimulation-Induced CA Model

After induction of anesthesia and placement of monitoring devices, the animals were allowed to equilibrate for 45 min to obtain a stable resting level. A temporary pacing lead was advanced into the right ventricle through the right sheathing canal and was connected to an electrical stimulator programmed in the S1S2 mode (300/200 ms), 40 V, 8:1 proportion, and 10-ms step length, to provide a continuous electrical stimulus until VF was induced.[10] VF was defined as an electrocardiogram showing waveforms corresponding to VF and a rapid decline in mean aortic pressure toward zero. After induction of VF, mechanical ventilation was discontinued.

CPR and Advanced Life Support

After 8 min of untreated VF, the animals were randomly assigned to one of the three groups (*n*=8 per group): SFI group (1 mL/kg), EPI group

(20 μg/kg), and normal saline (NS) group and received central venous injection, respectively. Mechanical ventilation and manual chest compressions (100 compressions/min, approximately one third of the anteroposterior chest diameter) were started immediately. CPR was performed by the same technician in all animals. The quality of chest compressions was controlled by a heartstart MRx monitor/defibrillator with Q-CPR. Ventilation was delivered by a bag respirator using ambient air, with a compression-to-ventilation ratio of 30:2. Only the principal investigator knew the group allocation of each animal. The investigators involved in resuscitation, data recording, data entry, and data analysis were blinded to the group allocations.

If VF persisted after 10 cycles of CPR (about 4 min), a 100 J (about 4 J/kg) shock (SMART Biphasic) was delivered. If the defibrillation attempt failed to achieve ROSC, manual chest compressions were rapidly resumed for another 2 min followed by a second defibrillation attempt. The second and subsequent shocks were delivered at 150 J. Resuscitation was continued until ROSC was achieved, or for longer than 30 min if ROSC was not achieved. ROSC was defined as a systolic blood pressure of >50 mm Hg sustained for at least 10 min. [11] If ROSC was not achieved within 30 min, the animal was considered dead. All animals received intravenous NS infusion [10 mL/(kg•h)] during anesthesia to replenish fluid losses.

After ROSC, the animals were mechanically ventilated with 100% oxygen. The vascular sheaths and endotracheal tube were removed after a 6-h period of intensive care. The animals were allowed to recover from anesthesia, and were placed in observation cages and monitored for another 18 h. The animals were then given intravenous propofol (100 mg) and were euthanized with a bolus intravenous injection of 10 mL of potassium chloride at 10 mol/L. Myocardial specimens were snap frozen in liquid nitrogen and stored at –80 ℃.

Hemodynamic Measurements

Hemodynamic data, including heart rate (HR), mean aortic pressure (MAP), right atrial pressure, and CO, were continuously recorded with a CO monitor. Serum lactic acid levels for which temperatures were corrected to 37 ℃ were measured regularly using an ABL 520 Blood Gas Analyzer (Radiometer Medical

ApS, Bronshoj, Denmark). The coronary perfusion pressure was defined as the difference between aortic diastolic pressure and right atrial diastolic pressure. Left ventricular +dp/dt and –dp/dt were measured to evaluate isovolumetric contraction and relaxation. Arterial and venous blood gases were measured at baseline, immediately after ROSC, and at 0.5, 1, 2, and 4 h after ROSC were measured at the same time points.

Measurements of Serum Catecholamine Levels

The serum levels of catecholamine, including dopamine (DA), EPI, and noradrenalin (NE), were measured by enzyme-linked immunosorbent assay using Quantikine immunoassays manufactured by R&D Systems (Minneapolis, MN, USA) according to the instructions provided with each kit.

Evaluation of Neurological Status

The neurological status of all surviving animals was evaluated at 24 h after ROSC using the porcine cerebral performance category (CPC) by two independent researchers who were blinded to the nature of the investigation. The CPC uses a 5-point scale to assess neurological function. [12] CPC 1 indicates normal neurological function, with animals having no difficulty standing, walking, eating or drinking, and being alert and fully responsive to environmental stimuli. CPC 2 indicates mild neurological disability, with animals able to stand but exhibiting an unsteady gait, drinking but not eating normally, and responding more slowly to environmental stimuli. CPC 3 indicates severe neurological disability, with animals unable to stand or walk without assistance, not drinking or eating, and being awake but not responding normally to environmental stimuli. CPC 4 indicates coma, and CPC 5 indicates brain death. CPC 1 or 2 was considered to be a favorable neurological outcome.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, Illinois, USA). Continuous variables are presented as mean $\pm$ standard deviation ($\bar{x} \pm s$). One-way repeated-measures ANOVA was used to determine differences over time within groups. Comparisons between groups were made with a one-way ANOVA, and Bonferroni's test was used for post hoc comparisons. The Fisher's exact test was used to
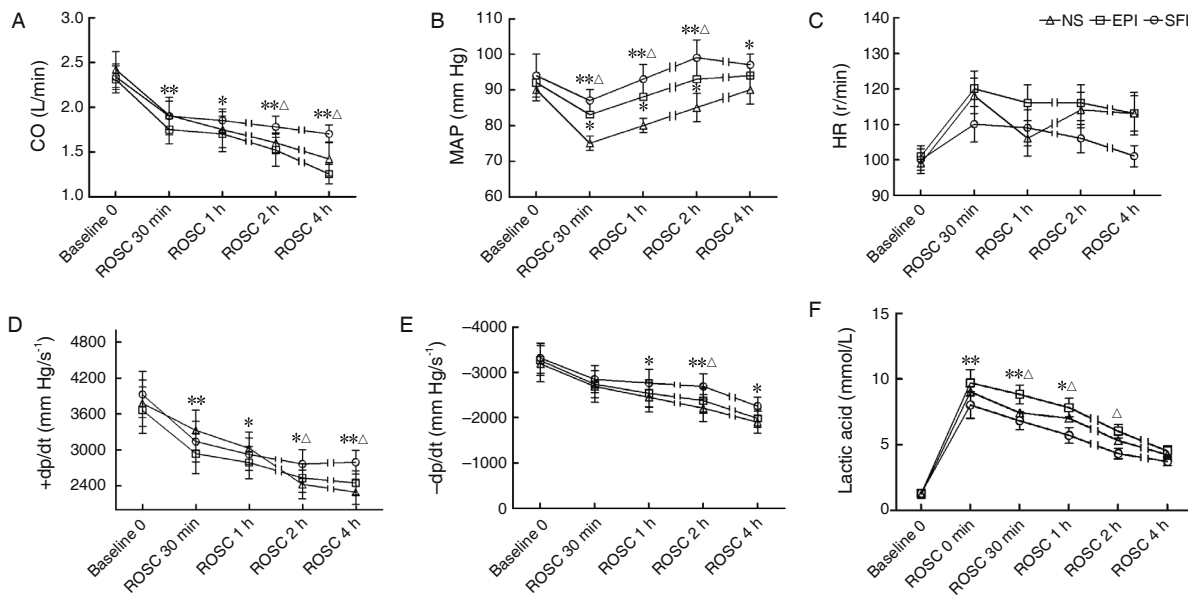
Figure 1.   Evaluation of Left Ventricular Function and Lactic Acid
Notes: A: CO; B: MAP; C: HR; D: +dp/d$_{tmax}$; E: -dp/dtmax; F: Lactic acid. $^{*}P<0.05$, $^{**}P<0.01$, compared with the baseline values; $^{\triangle}P<0.05$, compared with the NS group

compare discrete variables (ROSC, survival rates and favorable outcome survival rate). A two-tailed value of $P<0.05$ was considered to be statistically significant.

RESULTS

Resuscitation Outcomes

The weight among the NS, SFI and EPI groups was 30.31 ± 2.71, 30.42 ± 2.64 and 30.25 ± 2.86 kg, respectively. There was not significantly different among the three groups (all $P>0.05$). None of the variables (HR, MAP, and CO) differed significantly among the three groups ($P<0.05$, Figure 1). The resuscitation outcomes are shown in Table 1. There were no significant differences in ROSC rate, 24-h survival, or 24-h CPC among the three groups. All animals were successfully resuscitated, but the number of shocks and time to ROSC were significantly higher in the NS group than in the SFI and EPI groups ($P<0.05$). Five animals in the NS group survived for 24 h, and seven animals in the SFI and EPI groups survived for 24 h, which did not reach a significant difference in 24-h survival among the three groups. The rate of good

neurological function at 24 h was not significantly different among the three groups.

Evaluation of Left Ventricular Function and Lactic Acid Levels

As shown in Figure 1, at 4 h after ROSC, the HR was significantly lower in the SFI group than in the NS group ($P<0.01$), but was not significantly different between the EPI and NS groups. MAP was significantly higher in the SFI group than in the EPI and NS groups at 4 h after ROSC ($P<0.05$), but did not differ significantly among the three groups at other time points. The values of CO at 0.5, 1, 2 and 4 h after ROSC were significantly lower than those at baseline in the three groups (all $P<0.05$). At 1 and 2 h after ROSC the CO was not significantly different between the SFI and EPI groups; but at 4 h after ROSC the CO was significantly higher in the SFI group than in the EPI and NS groups ($P<0.05$), and was significantly lower in the EPI group than in the SFI and NS groups ($P<0.05$). At 4 h after ROSC, left ventricular +dp/dt and −dp/dt were significantly higher

Table 1.   Resuscitation Outcomes ($\bar{x} \pm s$)

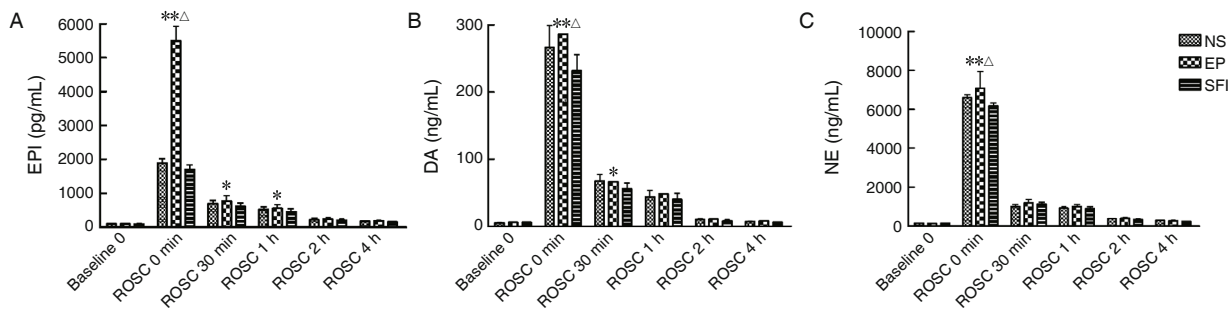| Group	n	ROSC success (n)	Shock times	CPR time (s)	Survival (n)		CPC (Scores)
					4 h	24 h	
NS	8	8	3.75 ± 1.49	450 ± 179	8	5	2.75 ± 1.39
SFI	8	8	$1.75 \pm 0.71^{*}$	$210 \pm 56^{*}$	8	7	2.38 ± 1.19
EPI	8	8	$2.00 \pm 0.76^{*}$	$210 \pm 72^{*}$	8	7	2.50 ± 1.20

Note: $^{*}P<0.05$, compared with the NS group

Figure 2.　Serum Catecholamine Levels ($\bar{x} \pm s$)
Notes: *$P<0.05$, **$P<0.01$, compared with the baseline values; $^{\triangle}P<0.05$, compared with the NS group

in the SFI group than in the NS group ($P<0.05$), and +dp/dt was significantly higher in the SFI group than in the EPI group ($P<0.05$). The lactic acid levels were significantly higher after ROSC than at baseline in all three groups (all $P<0.05$), peaking at 0.5 h and then gradually declining. At 4 h after ROSC, the lactic acid level was significantly lower in the SFI group than in the EPI and NS groups ($P<0.05$, Figure 1).

Serum Catecholamine Levels

The serum catecholamine levels were significantly higher after ROSC than at baseline in all three groups. Immediately after ROSC, the serum EPI level in the EPI group was significantly higher than in the SFI and NS groups (both $P<0.01$), which may be due to injection of EPI during CPR. In all groups, the serum EPI levels differed significantly among 1, 2, and 4 h after ROSC, which is consistent with the short half-life of the drug. The serum NE and DA levels were not significantly different between the EPI and SFI groups ($P>0.05$, Figure 2).

Correlations Between CO and Serum Catecholamine Levels

There were no correlations between CO or $\pm$ dp/dt and the serum levels of EPI, NE, or DA in any of the three groups. The correlation coefficients between CO and the serum levels of EPI, NE, and DA were −0.063, −0.040, and 0.042, respectively (all $P>0.05$); the correlation coefficients between dp/dt and the serum levels of EPI, NE, and DA were −0.109, −0.105, and −0.031, respectively (all $P>0.05$); and the correlation coefficients between −dp/dt and the serum levels of EPI, NE, and DA were −0.202, −0.135, and −0.102, respectively (all $P>0.05$).

DISCUSSION

The key findings of our study are as follows. First, both SFI and EPI increased coronary heart

pressure (CPP) and shortened the time to ROSC. Second, SFI tended to improve the hemodynamic status and oxygen metabolism compared to EPI in the first 6 h after ROSC. Third, there were no significant differences in NE or DA levels among the three groups, and there were no correlations between catecholamine levels and CO or dp/dt.

EPI is a nonselective α-adrenergic receptor (α1 and α2) and α-adrenergic receptor (α1 and α2) agonist. EPI induces venous vasoconstriction and contraction of skin, mucous membrane, renal artery, and small artery by its α-adrenergic receptor-mediated effects. It is therefore administered to make the blood flow from the periphery back to the central circulation, which directly enhances coronary perfusion pressur.[13] CPP is regarded as a predictor of ROSC and should be higher than 15 mm Hg to achieve ROSC.[14] EPI and SFI increased CPP in the present study, which might be an important cause of the shortened time to ROSC and decreased number of shocks. However, the vasopressor effect of SFI was milder than that of EPI.

CO decreased markedly in all groups after ROSC compared to baseline values, which showed post-resuscitation myocardial dysfunction. The time to ROSC is a predominant influence in post-resuscitation myocardial dysfunction.[15] SFI tended to improve the haemodynamic status and oxygen metabolism compared to NS in the first 6 h after ROSC. SFI is a typical form of Shenfu Decoction (参附汤) for intravenous medication, which main components include ginsenoside and aconitine.[16] The effects of SFI are based on aconitine properties, supplemented by ginsenoside, which can increase HR and myocardial contractility. Aconite contains noradrenaline salsolinol, which has excitatory effects on α-adrenergic receptors, therefore it can

significantly boost a reduction in coronary cerebral and peripheral vascular resistance by increasing coronary and cerebral blood flow.[17] In our previous study, SFI can reduce post-resuscitation myocardial dysfunction by modulating apoptosis and reducing impaired myocardial α-adrenergic receptor signaling,[18,19] which lead to higher CPP and shorter time to ROSC. The mechanism by which EPI increased the severity of post-resuscitation myocardial dysfunction was associated with its α-effects, by which the myocardial oxygen requirement was increased.[20]

CA is known to be a maximal stressor and the delivery of oxygen and metabolic substrates and removal of metabolites abruptly ceases with the onset of CA.[21] However, CPR only partially reverses this process. After ROSC from CA, the body must undergo a long period of systemic ischaemia-reperfusion, which is an unnatural pathophysiological state. The level of catecholamines is markedly elevated after ROSC, and endogenous catecholamines might result in severe vasoconstriction and microcirculatory shunting. Considering that injection of EPI may increase the levels of EPI and NE as well as affect blood pressure, only the EPI group received 0.02 mg/kg of EPI during CPR, and no other exogenous catecholamine or vasoactive drugs were used.

The serum catecholamine levels increased significantly after CPR and peaked after ROSC, which is consistent with the hemodynamic findings. The increased catecholamine levels during prolonged VF and early after ROSC may result from extensive ischemia in the body during CA, and from circulation of the catecholamines secreted by the adrenal medulla during chest compressions and after ROSC. Comparisons of the catecholamine levels among the three groups showed that the EPI level after ROSC was significantly higher in the EPI group than in the SFI and NS groups, but there were no significant differences in EPI level among the three groups at 0.5 h after ROSC, which reflects the short half-life of catecholamines. The NE and DA levels were also higher than the baseline levels at each time point after ROSC, but were not significantly different among the three groups, suggesting that these levels reflected elevation of endogenous catecholamine levels resulting from a stress response. The persistence of high catecholamine levels after the initial surge resulted from the hemodynamic instability and cardiac dysfunction after ROSC. After ROSC, the serum catecholamine levels decreased gradually, indicating that the initial stress response following CA decreased after ROSC, and confirming that increases in MAP and HR can not be maintained after ROSC without the use of vasoactive drugs. Our results did not show significant correlations between serum catecholamine levels and CO, +dp/dt, or −dp/dt, suggesting that endogenous catecholamine levels can not be used to predict outcomes after CPR.

Conflict of Interests

The authors declare no conflict of interests.

Author Contribution

Zhang D: conception and design of the research, drafting the manuscript and revising it critically for important intellectual content; Zhang Q: acquisition of data, analysis and interpretation of data; Li CS: giving final approval of the version to be published.

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