A Multi-center Randomized Controlled Clinical Study: Treatment in Septic Shock with Shen-Fu Injection

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参附注射液
让生命充满阳光

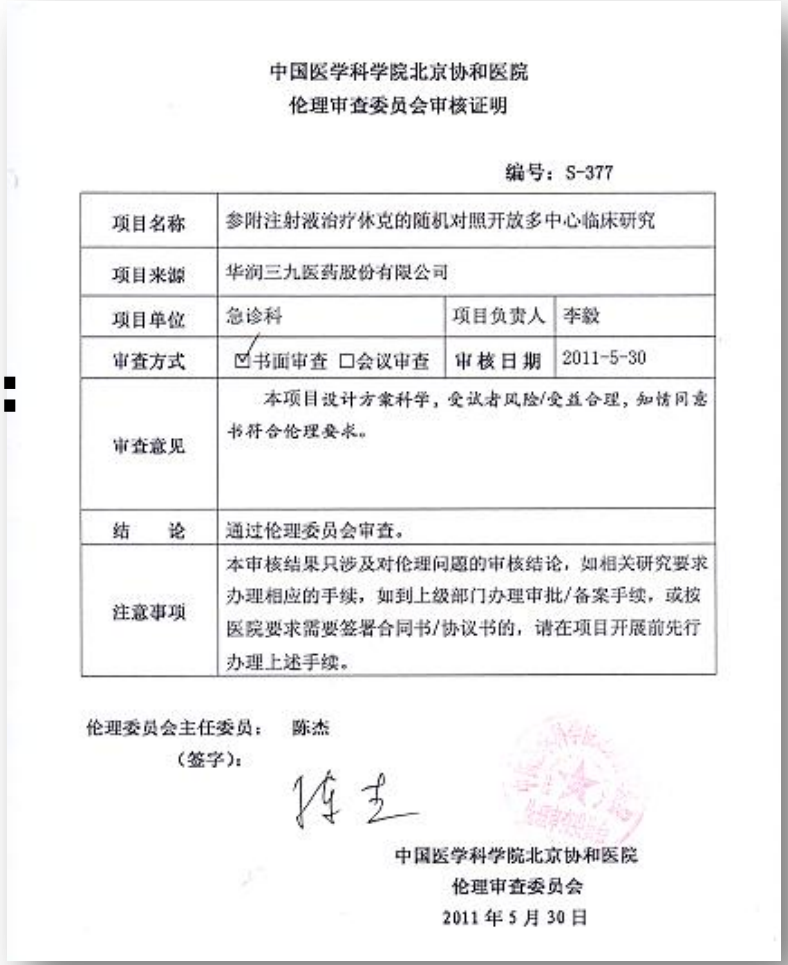
Ethics Review and Registration

Ethics Review Committee

- **Ethics Review No. (in China)：S-377**
- **Ethics Review No. (in English)：5-818**

Chinese Clinical Trial Register Centre

- **Registration No.：** ChiCTR-TRC-11001369



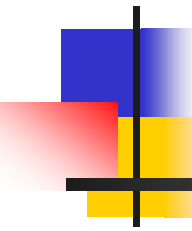
中国医学科学院北京协和医院
伦理审查委员会审核证明

编号：S-377

项目名称	参附注射液治疗休克的随机对照开放多中心临床研究		
项目来源	华润三九医药股份有限公司		
项目单位	急诊科	项目负责人	李毅
审查方式	☑书面审查 □会议审查	审核日期	2011-5-30
审查意见	本项目设计方案科学，受试者风险/受益合理，知情同意书符合伦理要求。		
结　论	通过伦理委员会审查。		
注意事项	本审核结果只涉及对伦理问题的审核结论，如相关研究要求办理相应的手续，如到上级部门办理审批/备案手续，或按医院要求需要签署合同书/协议书的，请在项目开展前先行办理上述手续。		

伦理委员会主任委员（签字）：陈杰

中国医学科学院北京协和医院
伦理审查委员会
2011 年 5 月 30 日



Section 1

Research Background

Dedicated to the Development of Chinese Emergency Medicine

The world is looking at China with great expectations in order to understand this country, that has been able to create a well-organized social system for its population-1.3 billion people, will be how to develop the modern first aid and resuscitation medicine, combined with traditional medicine.

----Professor Peter Safar

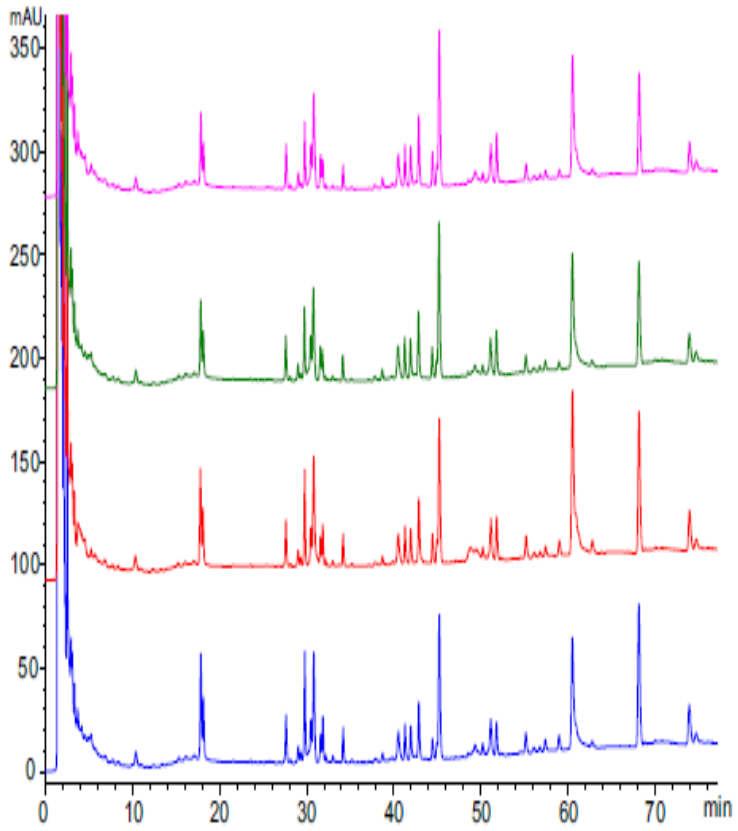
What is Shen-Fu Injection?

- Shen-Fu injection (SFI) is **an extract of traditional Chinese herbs**

- It is made from raw material of ginseng (Panax, family: Araliaceae) and fuzi (Radix aconiti lateralis preparata, Aconitum carmichaeli Debx, family: Ranunculaceae) by using multistage countercurrent extraction and macroporous resin adsorption technology.

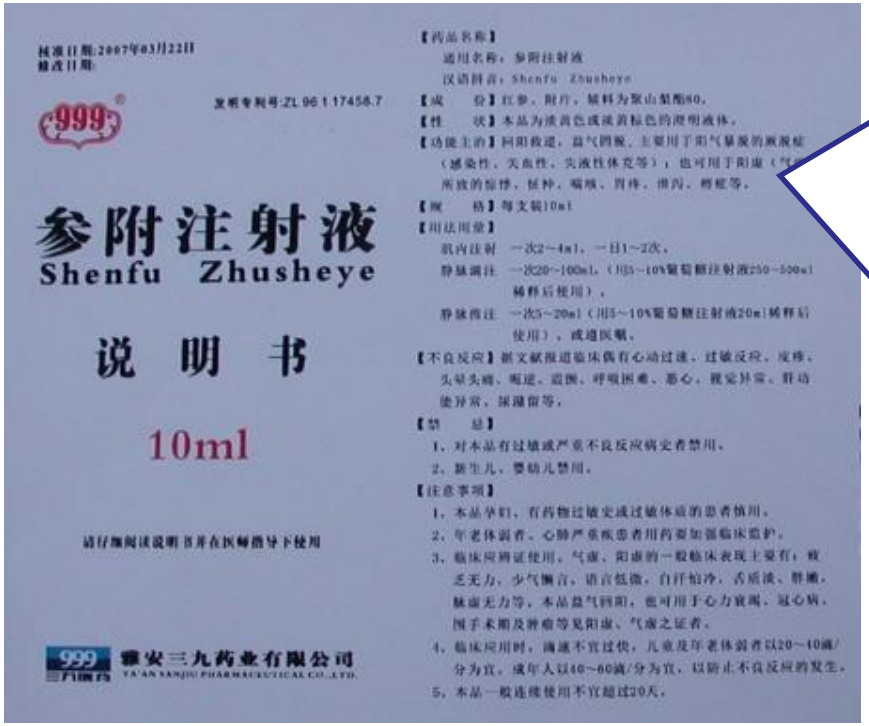
- The main components of SFI **include ginsenoside (0.8 mg/mL) and aconitine (0.1 mg/mL)**

Fingerprint Technology



- Fingerprint technology has been adopted in the process of production to ensure that the quality of Shen-Fu Injection is consistent over different batches

Description of Shen-Fu Injection



- Main Indications are Yang (Qi) deficiency cline due to the disease (blood loss, fluid loss, cardiac shock, septic shock)
- It can also be used the Yang (Qi) decline due to fright, palpitation, stomach pains, diarrhea, arthralgia

Research Background

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SHEN-FU INJECTION ATTENUATES POSTRESUSCITATION MYOCARDIAL DYSFUNCTION IN A PORCINE MODEL OF CARDIAC ARREST

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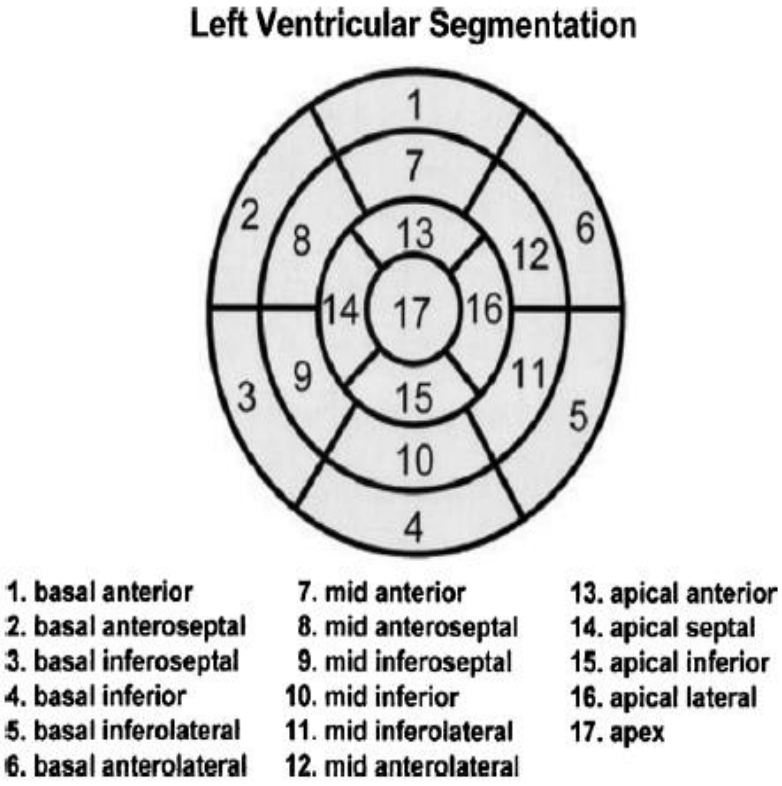
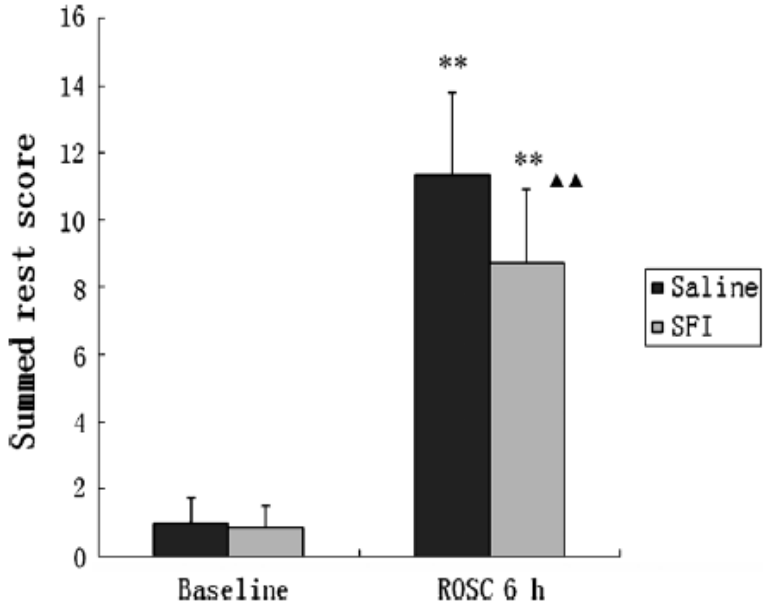
ABSTRACT—To investigate the effect of Shen-Fu injection (SFI) for the management of postresuscitation myocardial dysfunction in a porcine model of cardiac arrest. Ventricular fibrillation was induced electrically in anesthetized domestic swine. After 4 min of untreated ventricular fibrillation, cardiopulmonary resuscitation was initiated. Sixteen successfully resuscitated pigs were randomized to receive a continuous infusion of either SFI (0.24 mg/min) or saline placebo for 6 h, beginning 15 min after return of spontaneous circulation (ROSC). The SFI treatment produced better left ventricular $+dP/dt_{max}$, $-dP/dt_{max}$, cardiac output, and ejection fraction after ROSC. The SFI treatment also produced lower serum cardiac troponin I, lactate levels, and left ventricle malondialdehyde content after ROSC, whereas left ventricle superoxide dismutase, Na^+-K^+-ATPase, and Ca^{2+}-ATPase activity were significantly increased in the SFI group when compared with saline group. The cardioprotective effect of SFI was further confirmed by myocardial ultrastructure examination. Shen-Fu injection can attenuate postresuscitation myocardial dysfunction through beneficial effects on energy metabolism and remarkable antioxidant capacity.

KEYWORDS—Shen-Fu injection, postresuscitation myocardial dysfunction, cardiopulmonary resuscitation

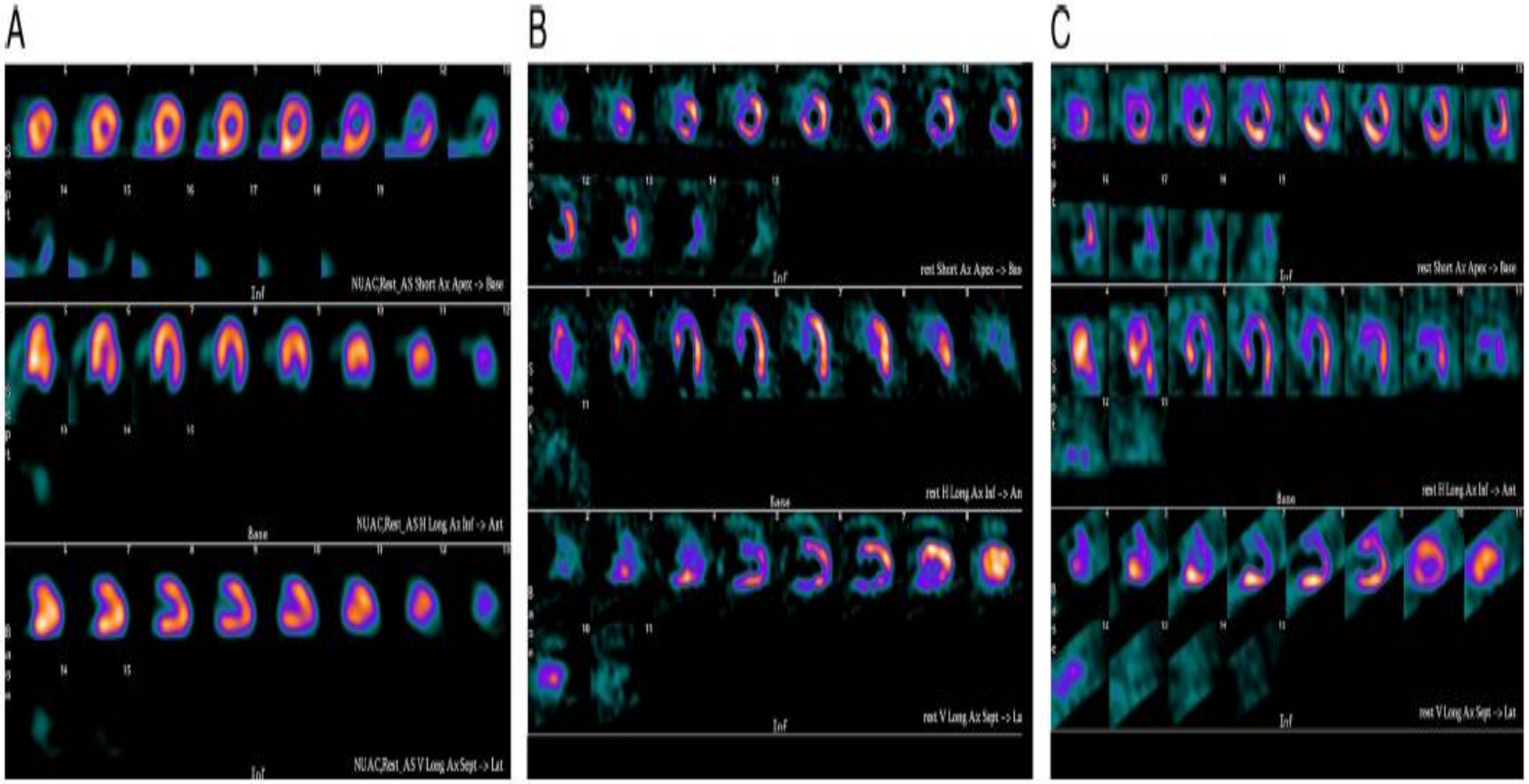
Myocardial Perfusion Study (Tc 99m MIBI) by SPECT





- **the SRS (summed rest score) was significantly decreased in the SFI group than in the saline group at 6 h after ROSC**

Examples Imaging of Porcine Cardiac Perfusion by Tc 99m MIBI SPECT at Baseline and 6 h after ROSC



Results

- Myocardial perfusion imaging showed that there were severe radioactive sparse defects in both groups at 6 h after ROSC, compared with the baseline (Fig. A)
- However, the SRS (summed rest score) was significantly decreased in the SFI group than in the saline group at 6 h after ROSC.
- Radioactive sparse defects were alleviated in animals treated with SFI (Fig. C).

Research Background

Experimental paper

Shen-Fu injection attenuates postresuscitation lung injury in a porcine model of cardiac arrest☆

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ABSTRACT

Objective: To investigate the effects of Shen-Fu injection (SFI) on postresuscitation lung injury in a porcine model of cardiac arrest.

Methods: Twenty-four anaesthetised male Landrace pigs were subjected to 4 min of untreated ventricular fibrillation (VF), followed by standard cardiopulmonary resuscitation. Sixteen successfully resuscitated pigs were randomised into two groups (eight pigs per group); one group received an SFI infusion and the other group received a normal saline infusion, at an infusion rate of 0.24 mg/min from 15 min after the return of spontaneous circulation (ROSC) until 6 h after ROSC.

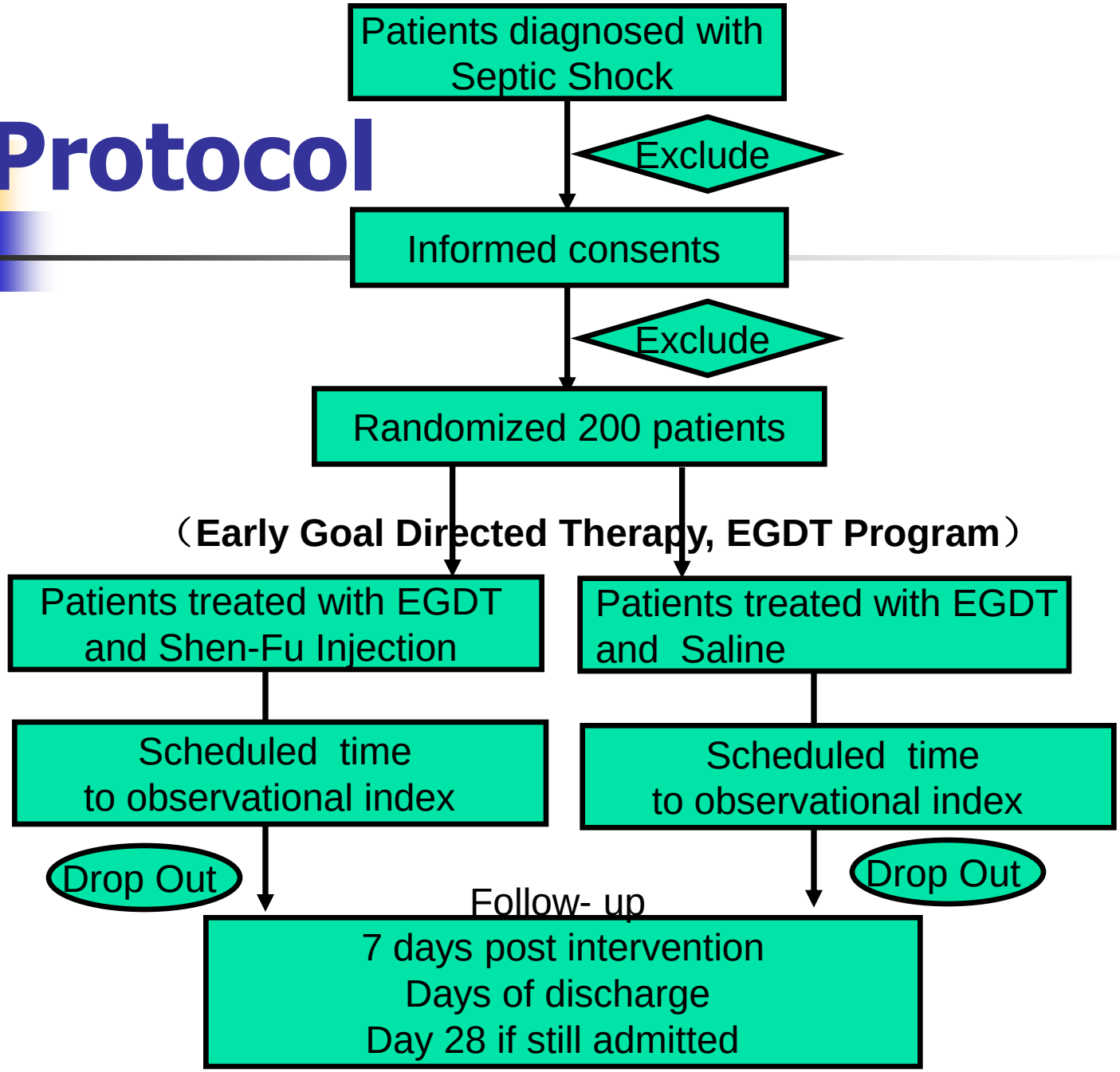
Results: Oxygenation index, respiratory index, oxygen delivery, oxygen consumption, oxygen extraction, dynamic lung compliance, airway resistance, external vascular lung water index, and pulmonary vascular permeability index at 15 min, 30 min, 1 h, 2 h, 4 h, and 6 h after ROSC were all worse than baseline in the saline group, and were all better in the SFI group than in the saline group. The pulmonary protective effects of SFI were further confirmed by histopathological and ultrastructural observations of lung tissue. SFI infusion resulted in lower apoptosis index, caspase-3 protein expression, and malondialdehyde content of lung tissue after ROSC, and increased Bcl-2 protein expression and superoxide dismutase, Na^+-K^+-ATPase, and Ca^{2+}-ATPase activity compared with the saline group.

Conclusion: Shen-Fu injection can attenuate postresuscitation lung injury through suppression of lung cell apoptosis and improvement of energy metabolism and antioxidant capacity.

Section 2

Research Protocol

Protocol


Patients diagnosed with Septic Shock
Exclude
Informed consents
Exclude
Randomized 200 patients
（Early Goal Directed Therapy, EGDT Program）
Patients treated with EGDT and Shen-Fu Injection
Patients treated with EGDT and Saline
Scheduled time to observational index
Scheduled time to observational index
Drop Out
Drop Out
Follow- up
7 days post intervention
Days of discharge
Day 28 if still admitted

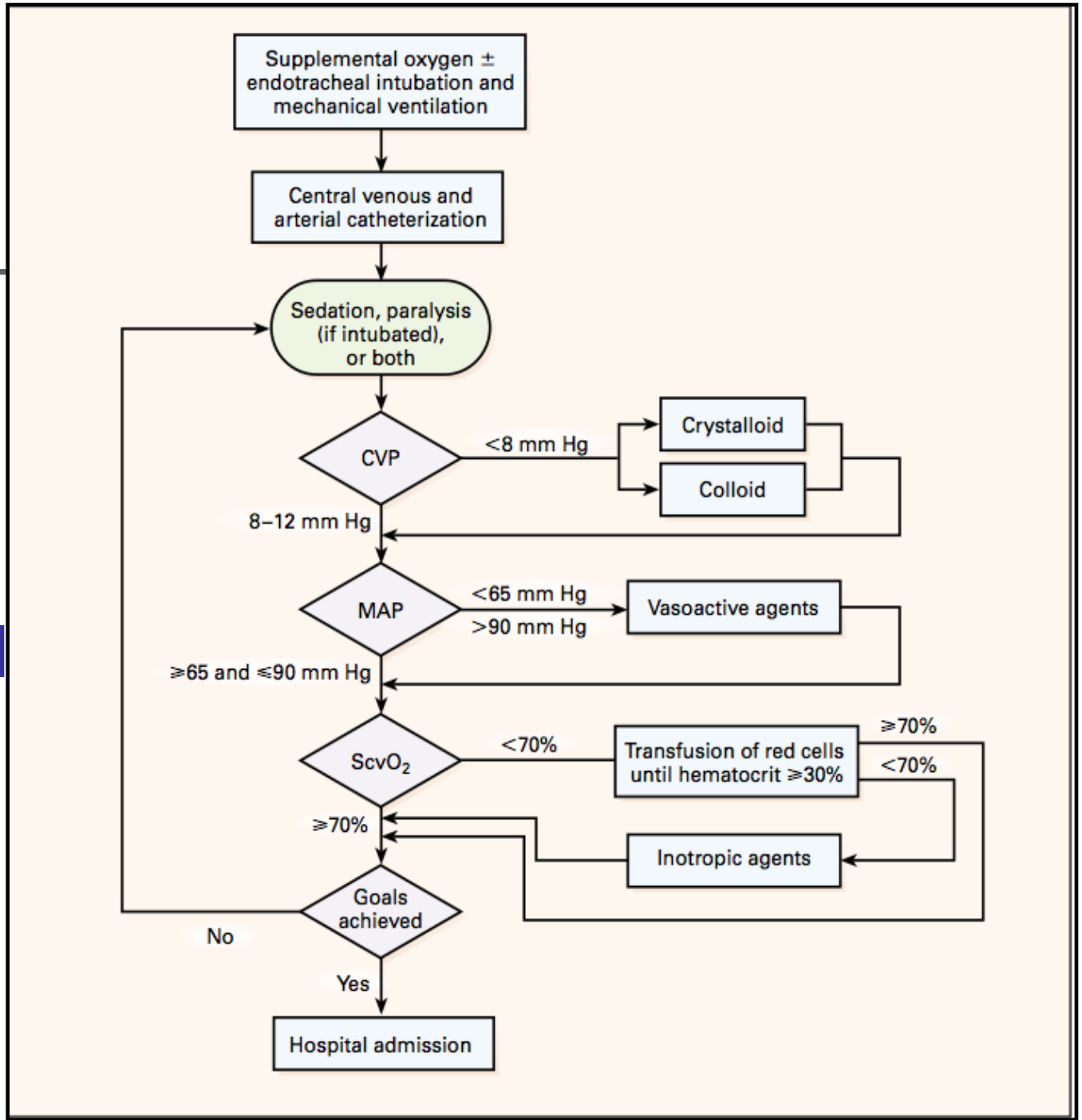
Included Subject

- A total of 200 septic shock patients (between June 2011 and December 2013) will be recruited from emergency department of nine hospitals.

Excluded Subject

- Age> 75years
- Poor Prognosis in 24 hours
- The need for surgery within 6 hours
- Pregnancy or breast-feeding women
- Applied with renal replacement therapy (such as hemodialysis,hemoperfusion) in the entire course of treatment

Early Goal Directed Therapy of Septic Shock



the Intervention Duration: 1+5 days

Intervention

EGDT

+ **Saline Injection**

First day :
Saline 50ml
intravenous injection within 10min
then Saline 50ml intravenous infusion in 20ml/h

Second day:
Saline 300ml intravenous infusion in 150ml/h. Q.D. 5 days

+ **Shen-Fu Injection**

First day :
Shen-Fu Injection 50ml
intravenous injection within 10min
then Shen-Fu injection 50ml
intravenous infusion in 20ml/h

Second day:
Shen-Fu injection 100ml + Saline 200ml intravenous infusion in 150ml/h. Q.D. 5 days

Schedule Time-Table

阶段 / 项目	筛选	入组	治疗期					随访	
访视	1	1	2	3	4	5	6	7	8
访视时间	0h	0h	6h	12h	24h	48h	6天	7天	28天
背景资料									
确定入选/排除标准	✓								
人口学资料	✓								
一般临床资料	✓								
诊断性观察									
Echo超声心动图		✓				✓			
病原学培养（仅感染性休克）		✓							
感染灶（仅感染性休克）	写出具体部位								
有效性观察									
生命体征等基本情况		✓	✓	✓	✓	✓	1次/1天		
血乳酸		✓	1次/3小时	✓	✓	1次 / 12小时	1次/1天		
血流动力学			1次/3小时	✓	1次/12小时				
血气分析		✓	✓	✓	✓	✓	✓		
炎性因子及NT-BNP/PCT		✓			✓	✓			
生化指标（肝肾功能）		✓		✓	✓	✓	✓		
心肌酶		✓	✓	✓	✓	✓	✓		
PCI时间（仅心源性）	仅记录（以小时为单位）								
休克指数		✓	✓	✓	✓	✓	1次/1天		
GCS评分		✓							
APACHE 2					✓				
安全性观察									
血常规及凝血功能		✓		✓	✓	✓	✓		
尿常规		✓				✓	✓		
便常规		✓							
心电图		✓			✓	✓	1次/1天		
记录不良事件			✓	✓	✓	✓	✓	✓	
其他									
随机分组		✓							
容量稳定时间（仅低血容量性）	按实际情况录入(小时)								
ICU住院天数	按实际情况录入（单位：天）								
总住院天数	按实际情况录入（单位：天）								
生存率								✓	✓
血管活性药物使用情况（单位时间内的总量，该时间点的血管活性药用量）			✓	✓	✓	✓	✓		

Assess Safety

- Vital Signs(T, R, BP, P, SPO2, consciousness)
- Blood Routine, Urine Routine, Stool Routine
- Liver function (ALT, AST), Renal function (BUN, Cr), Coagulation function , EKG

Adverse Event Reporting

- Tachycardia
- Rash
- allergic reactions
- Dyspnea
- dizziness, headache
- nausea, vomiting, hiccups
- muscle tremor

Assess Efficacy

- **The primary outcome measurements**

  Lactate Clearance Rate

- **The second outcome measurements**

  shock index return to normal time

  (shock index $\leq$ 0.8)

  Vasoactive medication usage (dopamine, norepinephrine)

Assess Efficacy

The primary endpoint

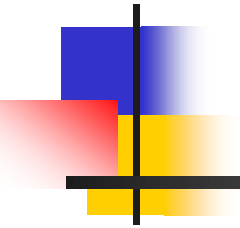
- all-cause mortality
- 7-day survival rate
- 28-day survival rate
- the length ICU stay

The second endpoint

- APACHE II score
- Glasgow score

Statistical Analysis

- An independent data and safety monitoring board has been established to review the data, assess the progress of the trial, particularly safety endpoint, including statistical analysis.



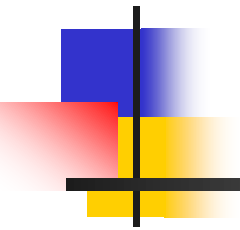
Safety ?

Yes

Assess Safety

- There were no deaths and no serious adverse events related to study medication.
- Occurrence rate of **mild** adverse events related to Shen-Fu injection is 1.06‰.

Effective ?



Assess Efficacy

- Until now, Seventy-six Septic Shock patients completed the study,

  39 randomized to Shen-Fu injection and 37 to saline. The clinical trial has not been finished yet.

- There were no significant difference in Lactate Clearance Rate within 6 hours and 12 hours in either group.

Assess Efficacy

- **The preliminary findings** suggested

  Shen-Fu injection have beneficial effects on septic shock. Compared with placebo, the shock index in the SFI group was significantly alleviated at 12 h after intervention.

Assess Efficacy

- The 7-days survival rate in Shen-Fu Injection was 7% higher than that in placebo group.
- Shen-Fu Injection also improved 28- days survival rate.


thanks