

# Effect of Yangyin Shuxin Decoction on Exercise Capacity in Patients with Heart Failure with Normal Ejection Fraction: Rationale and Design of a Randomized Controlled Trial

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## Study protocol

**Keywords:** heart failure, Yangyin Shuxin Decoction, traditional Chinese medicine, randomized controlled trial

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## Abstract

**Background** The incidence of heart failure with normal ejection fraction (HFNEF) is increasing yearly, accounting for approximately half of all heart failure cases. Even after standardized treatment, the patient's prognosis is not good. Therefore, it is necessary to explore new treatment methods for HFNEF. Yangyin Shuxin Decoction, a traditional Chinese medicine prescription from our clinical experience in the treatment of HFNEF, has a potential cardioprotective effect. Preliminary clinical trials have shown that this prescription can improve the quality of life of HFNEF. This prompted us to use more objective indicators to further evaluate whether Yangyin Shuxin Decoction can improve the exercise capacity in HFNEF patients.

**Methods** This is a single-center parallel randomized controlled trial. The 64 patients who met the inclusion criteria were from the Cardiovascular Clinic. They will be randomly assigned to the treatment group (Yangyin Shuxin Decoction combined with standard treatment) or the control group (standard treatment) according to the ratio of 1:1. The course of treatment will be 2 weeks. Both groups were interviewed at the following time points: at enrollment (V1), and week 2 (V2), week 4 (V3), week 8 (V4), and week 12 (V5) after enrollment. The primary indicator is the peak oxygen consumption (Peak VO<sub>2</sub>) of the cardiopulmonary exercise test (CPET). Secondary indicators include CPET indicators such as anaerobic threshold oxygen consumption, carbon dioxide ventilation equivalent slope, echocardiographic indicators such as the ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity (E/e'), left atrial volume index (LAVI), left ventricular mass index (LVMI), the peak velocity of tricuspid regurgitation (TR), B-type natriuretic peptide (BNP), New York Heart Association (NYHA) cardiac function grading, and so on. These indicators will be used to evaluate the effect of Yangyin Shuxin Decoction on exercise capacity in patients with HFNEF.

**Discussion** At present, it is unclear whether the exercise capacity can be maintained after long-term use of Yangyin Shuxin Decoction. In this study, we will evaluate whether Yangyin Shuxin Decoction can improve the exercise capacity and quality of life of patients with HFNEF. This will provide an objective basis for the therapeutic effect of traditional Chinese medicine on HFNEF.

## Background

China gradually enters an aging society and the incidence of heart failure with normal ejection fraction (HFNEF) is increasing yearly.<sup>1</sup> These patients account for approximately half of all patients with heart failure (HF).<sup>2-4</sup> Beta-adrenergic receptor blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and so on are routinely used to treat HFNEF. However, they have not improved the prognosis and reduced the mortality of patients with HFNEF.<sup>5-7</sup> Patients with HFNEF who received conventional treatment still have problems, such as low exercise capacity and low quality of life.<sup>8</sup> Previous clinical studies<sup>9-12</sup> suggested that traditional Chinese medicine (TCM) had certain efficacy in relieving symptoms, increasing activity capacity, improving quality of life, and other aspects in patients with HFNEF. However, the quality of these studies is poor. Some deficiencies reduce the level of evidence such as large differences in the study population, unclear inclusion/exclusion criteria, non-uniform TCM syndromes, relatively single clinical evaluation indicators, and other problems.<sup>13</sup>

Yangyin Shuxin Decoction is a TCM prescription for treating HFNEF. It has the effects of nourishing Yin (Yangyin), promoting blood circulation (Huoxue), and clearing away heat (Qingre). Preliminary clinical trials have proved that it can improve the quality of life of patients with HFNEF.<sup>14</sup> The single drug component of each drug in the prescription has multiple targets to improve the heart and lung functions and increase the exercise capacity. Hence, we planned to use more objective indicators to further evaluate whether Yinyin Shuxin can improve the exercise capacity of patients with HFNEF.

We hypothesized that Yangyin Shuxin Decoction could improve the exercise capacity of patients with HFNEF. Moreover, we designed this randomized controlled trial to compare the efficacy of conventional western medicine and Yangyin Shuxin Decoction combined with conventional western medicine on exercise capacity in patients with HFNEF. The relevant design principles and implementation schemes of the randomized controlled trial protocol are as follows.

Figure 1

## Methods

### *Study design*

This is a single-center, prospective, parallel, randomized controlled trial. Based on a computer-generated randomized number, 64 patients with HFNEF will be randomly assigned to either the treatment or control group. Patients in the treatment and control groups will be treated with a drug intervention for 2 weeks and followed up for 12 weeks. We will terminate this test when the following situations occur: 1) a serious safety incident occurred during the test; 2) there are major errors in the clinical trial protocol; 3) serious deviations occur so that it is difficult to evaluate the efficacy of the drug; and 4) the project management department cancels the test. A data monitoring committee will be established, mainly to make interim analysis and assess adverse events. The committee will review the core trial processes and documents, and discuss any amendments to the main study protocol. Any adverse event will be recorded in the CRF and reported to the data monitoring committee in a timely manner. We will provide appropriate compensation for any injured subjects. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is provided as Additional file 1.

### *Participants*

All of the 64 patients with HFNEF will be enrolled in the Department of Cardiology, the First Teaching Hospital of Tianjin University of TCM. First, the patients will be fully introduced to the benefits and risks of the treatment. Second, the patients need to sign the informed consent on a voluntary basis. Then, the patients will be divided into the treatment (Yangyin Shuxin Decoction combined with the standard treatment) or control (standard treatment) groups according to the coding sequence from the pre-set random number table. The inclusion and exclusion criteria are shown in Table 1.

### **Table 1. Eligibility criteria**

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**A. Inclusion criteria**

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1. Age > 40 years;
2. Patients with the following symptoms and/or signs:

1 Symptoms: shortness of breath or weakness or reduced exercise endurance or dyspnea at night or orthopnea;

2 Signs: jugular hypertension, hepatojugular reflux, galloping rhythm, cardiac hypertrophy, weight gain, peripheral edema, or pulmonary rales

3. LVEF  $\geq 50\%$

4. BNP > 35 pg/mL

5. Meet at least one of the following criteria:

1 There are cardiac structural changes: left atrial enlargement (LAVI > 34 ml/m<sup>2</sup>) or left ventricular hypertrophy (LVMI: male > 115 g/m<sup>2</sup>, female > 95 g/m<sup>2</sup>);

2 Diastolic dysfunction: E/e'  $\geq 13$  and e'  $\leq 9$  cm/s;

6. Sign the informed consent

**B. Exclusion criteria**

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1. Acute coronary syndrome, congenital heart disease, severe valvular disease, constrictive pericarditis, hypertrophic cardiomyopathy, and restrictive cardiomyopathy;
  2. Patients with history of intracoronary stent implantation, permanent pacemaker, implantable defibrillator (ICD), or left ventricular assist device implantation or coronary artery bypass grafting within nearly 90 days;
  3. Systolic pressure > 160 mmHg or < 90 mmHg at intake;
  4. Chronic lung disease requiring oxygen therapy or drug intervention;
  5. Cerebral infarction within 90 days;
  6. Special treatments should be used for patients with comorbidities such as severe liver or renal failure and malignant tumor, which could influence the clinical treatment of HFNEF;
  7. Pregnant or breastfeeding women, or women at childbearing age without reliable methods of contraception;
  8. Unable to complete cardiorespiratory exercise test;
  9. Poor patient compliance;
  10. Participated in other studies within 2 months
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The follow-up period was 12 weeks. A full physical examination and assessment of adverse events will be performed for all participants. After the patient signs the informed consent form, we will collect general information including demographics, medical history, and concomitant medications. Two clinical controls were performed at the time of enrollment (V1) and week 2 (V2). Indicators include cardiac ultrasound, CPET, BNP, NYHA cardiac function grading, EQ-5D-5L, TCM four-diagnostic information score, syndrome judgment, blood pressure, heart rate, weight, and so on. Blood and urine samples will also be taken. During the follow-up period, the investigator will contact the participants via telephone at weeks 4 (V3), 8 (V4), and 12 (V5) to monitor the patient's blood pressure, weight, NYHA cardiac function, hospitalization/outpatient costs, and compound endpoint events to assess the patients' quality of life. This program was prepared in accordance with the standard protocol project SPIRIT 13. The specific process of the study is shown in Table 2.

**Table 2. Research access flow chart**

Study phase	Screening/enrolment	Follow-up			
Items					
Time	Baseline	Week 2	Week 4	Week 8	Week 12
Visit	V1	V2	V3	V4	V5
Confirm eligibility	Ö				
Written informed consent	Ö				
Data collection					
General data	Ö				
Medical history	Ö				
Physical examination	Ö	Ö			
Current medications	Ö	Ö			
Dispense drugs	Ö				
Record drug recall		Ö			
Compliance judgment		Ö			
Observation of efficacy					
CPET	Ö	Ö			
Echocardiography	Ö	Ö			
NYHA classification	Ö	Ö	Ö	Ö	Ö
EQ-5D-5L	Ö	Ö			
TCM 4 diagnostic information	Ö	Ö			
Chinese medical syndrome elements	Ö	Ö			
BNP, BUA	Ö	Ö			
UAlb, Cr, UAlb/Cr	Ö	Ö			
Endpoint event		Ö	Ö	Ö	Ö
Hospitalization/outpatient costs			Ö	Ö	Ö
Safety observation	Ö	Ö	Ö	Ö	Ö
Blood pressure, heart rate, weight	Ö	Ö	Ö	Ö	Ö
Blood tests	Ö	Ö			
CR, BUN, ALT	Ö	Ö			
Electrolyte	Ö	Ö			
Adverse events	Ö	Ö	Ö	Ö	Ö
Study completion status					Ö

CRF examination					Ö
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Note: BUA: blood uric acid; UAlb: urine microalbumin; CRF: case report form.

### ***Interventions***

Other TCM preparations are not allowed during the washout period for two weeks. The patients in the treatment group will be treated with conventional western medicine combined with Yangyin Shuxin Decoction 150 ml, twice a day. All Chinese herbal medicines in Yangyin Shuxin Decoction are from the Department of Pharmacy, the First Teaching Hospital of Tianjin University of TCM. The decocting room is uniformly fried and made into a vacuum package of 150 ml. The remaining decoction will be recycled if the participants withdraw from the test midway. The patients in the control group will receive conventional western medicine treatment. The duration will be 2 weeks. Both groups will be interviewed at the following time points: enrollment (V1), week 2 (V2), week 4 (V3), week 8 (V4), and week 12 (V5) after enrollment.

The TCM theory believes that patients with HFNEF have clinical syndrome characteristics of yin deficiency, blood stasis, and internal heat.<sup>15</sup> Each of the single-drug ingredients in Yangyin Shuxin Decoction includes a variety of compounds such as polyphenols, terpenoids, saponins, and alkaloids that are beneficial to the cardiovascular system. The relevant bioactive ingredients and potential mechanisms are shown in Table 3. These ingredients have the combined effects of improving heart and lung functions, increasing activity tolerance, improving microcirculation, and improving immunity and body antioxidants in patients with HFNEF.

Western medicine standard treatment plan is implemented according to the “China Heart Failure Diagnosis and Treatment Guide 2014”<sup>16</sup> and “2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure”<sup>17</sup>. The Western medicine standard treatment includes health education for patients to help them establish a heart-healthy lifestyle (such as salt restriction, water restriction, weight monitoring, physical exercise, smoking cessation, alcohol withdrawal, and so on) and medication guidance and emergency management instructions. In addition, other TCMs for the treatment of cardiovascular diseases should be avoided.

**Table 3. Cardiovascular effects and potential mechanisms of active ingredients**

Herbs	Bioactive ingredients	Beneficial effects	Potential mechanisms	Ref. #
<i>Fructus corni</i>	<i>Cornus officinalis</i> saponins	Anti-inflammatory; protecting the cardiovascular and cerebrovascular system; inhibiting myocardial cell apoptosis; reverse cardiac hypertrophy	Decreasing the activity of serum CPK and LDH; decreasing the expression of P47phox and Nox4 in the myocardium	18,19
<i>Radix Ophiopogonis</i>	Total saponins of Ophiopogon; Polysaccharide MDG-1 from <i>Ophiopogon japonicas</i> ;	Promoting myocardial injury, healing and narrowing the infarction and necrotic areas	Reducing malondialdehyde and free fatty acids; effects on the pituitary adrenocortical system	20,21
<i>Rhizoma Polygonatum</i>	Ophiopogon D PP; EE of Rhizoma Polygonatum	Inhibiting myocardial cell apoptosis; enzyme inhibition, anti-inflammation, anti-oxidation	Inhibiting the release of various enzymes; increasing SOD activity and decreasing MDA content	22
<i>Coptidis rhizoma</i>	Alkaloids; berberine	Positive inotropic action; vasodilatation; heart cell protection; antiapoptotic	Blocking K <sup>+</sup> channels; activating AMP protein activated protein kinase and P13K/Akt pathways	23,24
<i>Carapax trionycis</i>	<i>Trionyx sinensis</i>	Resistance to hypoxia;	Increasing the	

	polysaccharides;	improving immune function	activity of LDH	25
	<i>Trionyx sinensis</i> extract (TSWE)			
<i>Radix Salviae miltiorrhizae</i>	Terpenoids	Antiatherogenic;	Inhibiting the calcineurin/NFAT pathway;	26,27
	Tanshinones	cardiac cytoprotective; antioxidant; anti-inflammatory; antithrombotic	antiapoptosis	
<i>Lumbricus</i>	Unsaturated fatty acid	Thrombolysis and anticoagulation;	Reducing platelet adhesion and prolonging thrombosis;	28
	Vaccenic acid			
	arachidonic acid	Antihypertensive;		
	Platelet-like activating factor	regulation of the immune	Inhibiting ACE activity	
	<i>Lumbricus peptides</i>			
<i>Rhizoma pinelliae</i>	Alkaloids	Anti-arrhythmia;	Decreasing the activity of serum lactate dehydrogenase and phosphocreatine kinase;	29-31
	Organic acids	increase coronary flow;		
	Volatile oils			
	$\beta$ -stanols	protecting the heart ischemia reperfusion injury and vascular endothelial cell injury	Inhibiting LPS stimulates endothelial cells to secrete the inflammatory cytokines, interleukin-6 and	

<i>Trichosanthes peel</i>	Volatile oils amino acids flavonoids	Anti-myocardial ischemia; anti-atherosclerosis; protecting vascular endothelium; dilating blood vessels; resistance to hypoxia	tumor necrosis factor-alpha Enhancing free radical scavenging ability; decreasing INOS activity and NO synthesis and free radical formation	32
<i>Fructus Aurantii</i>	Alkaloid synephrine N- methyltyramine flavonoids hesperidin Nobisexualletin	Raising blood pressure; anti-atherosclerosis; inhibiting thrombosis	Promoting- adrenalin secretion indirectly; maintaining osmotic pressure; inhibiting vascular sclerosis	33

Note: CPK: creatine phosphokinase; LDH: lactate dehydrogenase; PP: polygonatum polysaccharide; EE: ethanol extract; SOD: superoxide dismutase; MDA: malondialdehyde; AMP: adenosine monophosphate; K<sup>+</sup>: calcium ion; P13K: phosphatidylinositol 3-kinase.

## Outcomes

**Primary outcome:** the change of Peak VO<sub>2</sub> in cardiopulmonary exercise test .

**Secondary outcomes:**

□ anaerobic threshold and ventilatory equivalent for carbon dioxide (VE/VCO<sub>2</sub>) slope detected in the cardiopulmonary exercise test.

□ E/e', LAVI, LVMI, and TR detected with ultrasonic cardiogram.

□BNP, NYHA cardiac function grading, EQ-5D-5L, TCM four-diagnostic information score, syndrome judgment, compound endpoint events, and so on.

**Security outcomes:** Vital signs, some laboratory tests, and adverse events are considered as safety outcomes. Vital signs, including blood pressure and heart rate, routine laboratory tests (routine urinalysis, routine blood test, and hepatic and renal functions), and electrocardiograms, and the adverse events will be documented at each visit.

### ***Patient and public involvement***

The patients or the public were not involved in the design or in conducting, reporting, or disseminating our research.

### ***Sample size***

The sample size is computed based on the literature “Effect of If-channel inhibition on hemodynamic status and exercise capacity in heart failure with preserved ejection fraction: a randomized trial”,<sup>34</sup> peak VO<sub>2</sub> on day 7 is 3.0±3.6 ml/kg/min in the treatment group and 0.4±2.7 ml/kg/min in the control group. Sixty-four patients will be recruited with a single-sided alpha of 0.05, a power (1-β) of 0.90, and a dropout rate of 20%. The calculation formula is as follows<sup>35</sup>:

[See supplementary files for formula.]

### ***Blinding***

Blinding the researchers responsible for the implementation and patients included is not possible due to the particularity of dosage forms. The investigators are responsible for distributing the drugs. To ensure the reliability of the test, the personnel and statistical experts performing the outcome index evaluation will be blinded. All research team members were instructed not to communicate with the participants regarding their allocation.

### **Data collection and management**

To assess the patients’ health status since the last visit and HFNEF-related re-hospitalization or unplanned medical conditions throughout the study period, the two groups will be contacted every 2 weeks or a month. All original data will be observed directly by clinical researchers and documented completely and timely in the case report form (CRF), including the reasons why patients cannot participate. To ensure the reliability of data, the CRF will be entered by the double-entry method. All

errors will be crossed out and corrected and signed by the corresponding investigator. All these data will be locked in a separate cabinet. Only authorized investigators are permitted to access this information.

## **Statistical analysis**

SPSS23.0 statistical analysis software will be used to calculate the test data, and descriptive statistics will be conducted for all the data. For the differences between the test groups, chi-square test will be used for the counting data. The t-test will be applied when normality (and homogeneity of variance assumptions) is satisfied, otherwise the rank sum test will be used.

The number of screened patients and reasons for exclusion will be reported, as well as protocol violations and reasons. An effectiveness analysis will be conducted using the randomized populations. Participants who have received treatment but there is no valid evaluation data will be considered as missing and will be included in the effectiveness analysis.

## **Discussion**

To the best of our knowledge, this is the first randomized controlled trial using cardiopulmonary exercise test indexes to evaluate the impact of TCM on the exercise capacity of patients with HFNEF. Cardiopulmonary exercise test indicators (including peak VO<sub>2</sub>, anaerobic threshold, VE/VCO<sub>2</sub> slope, and so on) are taken as the main indicators, and combined with echocardiography, BNP, NYHA cardiac function grading, generic EQ-5D-5L, and other indicators normally used to evaluate the prognosis of patients with HFNEF, to comprehensively evaluate the prognosis of HFNEF patients. Peak VO<sub>2</sub>, the main efficacy indicator, is an important indicator to evaluate the aerobic work ability of the human body. Not only can it be used to evaluate the severity of HFNEF and the effect of cardiac rehabilitation training, but also closely related to the long-term prognosis of patients.<sup>36-38</sup> Peak oxygen consumption is also an effective and practical evaluation index of aerobic capacity and has good retest reliability.<sup>39</sup> The anoxia threshold, a secondary therapeutic index, can reflect the body's potential to tolerate load. It is usually measured by sub-maximum exercise and is rarely affected by subjective and objective factors. It can sensitively show the balance of tissue oxygen supply and demand and accurately evaluate the anoxia metabolic capacity and cardiopulmonary function during exercise.<sup>40</sup> In addition, Nedeljkovic<sup>41</sup> observed that, in HFNEF patients undergoing cardiopulmonary exercise test combined with exercise load ultrasound, the equivalent slope of carbon dioxide ventilation (VE/VCO<sub>2</sub> slope) was an independent predictor of HFNEF prognosis. At the same time, the echocardiographic index E/e' was used to evaluate cardiac diastolic function, left atrial pressure, and left ventricular filling pressure volume curves, which were estimated by this method to be very close to those of the invasive catheterization method; and it is not affected by ejection fraction and cardiac arrhythmias and has now been designated as one of the main ultrasonic screening parameters of HFNEF by the guidelines.<sup>42</sup>

In addition, during the follow-up period of 3 months, patients' clinical conditions, especially regarding the re-hospitalization rate and the outpatient and inpatient costs will be tracked to comprehensively evaluate the patients'

exercise capacity and quality of life. At present, it is unclear whether the exercise capacity can be maintained after the long-term use of Yangyin Shuxin Decoction. Even so, this study will provide valid data for TCM to improve the exercise capacity of patients with HFNEF. Although it cannot fully explain the multi-linked interventional and pharmacological mechanism of TCM decoction on HFNEF, we can still use it as an intervention method and explore the mechanism from the perspective of pathophysiology in the future, because the fact that it can improve exercise tolerance in patients with HFNEF has been proven.

In conclusion, this is a single-center parallel randomized controlled trial. We will evaluate whether Yangyin Shuxin Decoction can improve the exercise capacity and quality of life of patients with HFNEF. This will provide an objective evidence for the therapeutic effect of TCM on HFNEF.

## **Trial Status**

This trial is currently recruiting participants (protocol version 1.1, 10 November 2017). The study will run from 1 December 2017 to 30 June 2021.

## **List Of Abbreviations**

**HFNEF:** Heart failure with normal ejection fraction

**Peak VO<sub>2</sub>:** The peak oxygen consumption

**CPET:** Cardiopulmonary exercise test

**E/e':** the ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity

**LAVI:** Left atrial volume index

**LVMI:** Left ventricular mass index

**TR:** The peak velocity of tricuspid regurgitation

**BNP:** B-type natriuretic peptide

**NYHA:** New York Heart Association

**ACEI:** Angiotensin-converting enzyme inhibitors

**ARB:** Angiotensin II Receptor Blockers

**TCM:** Traditional Chinese medicine

**LVEF:** Left ventricular ejection fraction

**EQ-5D-5C:** EuroQol-5 Dimension- 5 Level

**BUA:** Blood uric acid

**UA1b:** Urine microalbumin

**CR:** Creatinine

**BUN:** Blood urea nitrogen

**ALT:** Alanine transaminase

**CRF:** Case report form

**ESC:** European Society of Cardiology

**CPK:** Creatine phosphokinase

**LDH:** Lactate dehydrogenase

**PP:** Polygonatum polysaccharide

**EE:** Ethanol extract

**SOD:** Superoxide dismutase

**MDA:** Malondialdehyde

**AMP:** Adenosine monophosphate

**K<sup>+</sup>:** Calcium ion

**P13K:** Phosphatidylinositol 3-kinase

## Declarations

**Acknowledgement:** We thank all the participants in our study.

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### Authors' contributions

JM made substantial contributions to the concept and design of the clinical trial. ZZ and XW were responsible for the design, implementation, and management of the study and manuscript writing, and contributed equally to the article. SW is responsible for specimen preservation, inspection, and determination. RZ is in charge of ultrasonic testing. YL is responsible for the operation of the cardiopulmonary exercise test. QS was responsible for patient inclusion. SL and TC participated in the research scheme formulation and thesis writing. QL and HL participated in the manuscript writing, case inclusion, and patient follow-up.

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**Availability of data and materials:** The datasets generated and analysed during the current study will be available from the corresponding author or chief investigator on reasonable request.

**Ethics approval and consent to participate:** The study will be conducted according to the principles of the Helsinki Declaration. The Research Ethics Committee of the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine have approved the study. If there is any modification of the protocol and informed consent, or changes of the

principal investigator during the study, it will be submitted to the ethics committee for re-reviewing. All participants will be informed about the details of the trial, including the purpose, arrangement, probable risks and benefits. And signed informed consent will be obtained from all participants before enrolment.

**Consent for publication:** Not applicable.

**Competing interests:** The authors declare that they have no competing interests.

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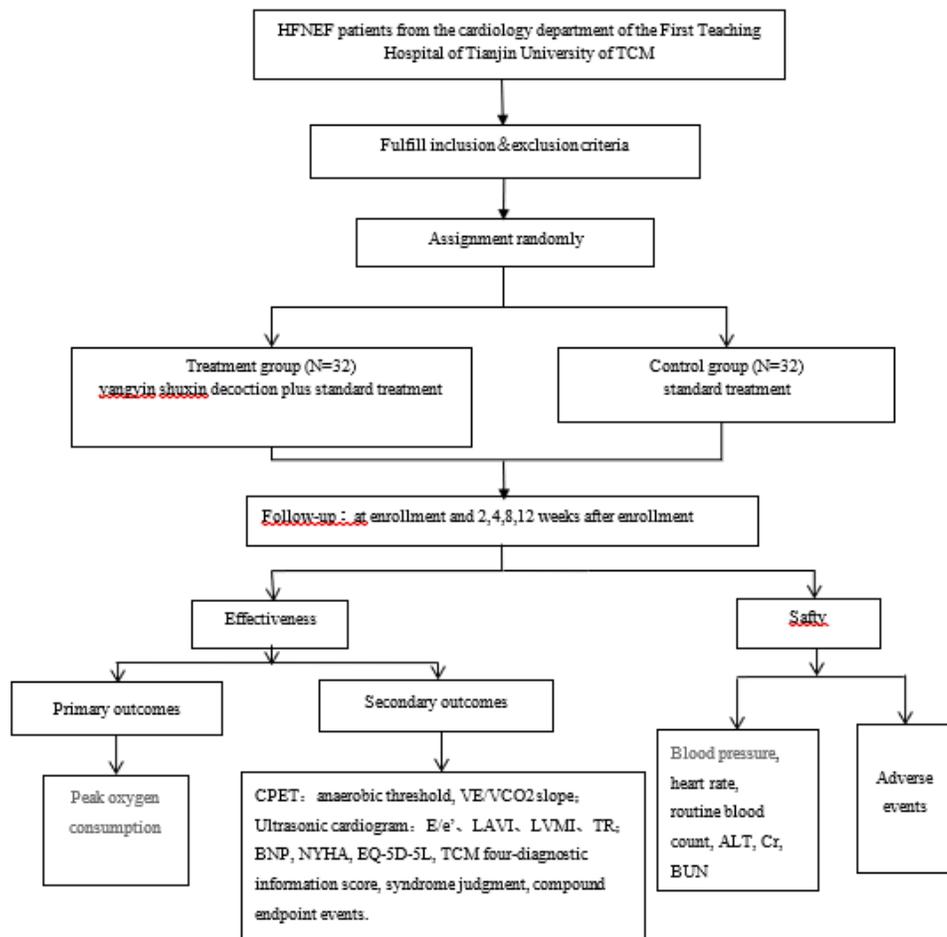
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## Figures



**Figure 1**

Study flow chart. Note: CPET: cardiopulmonary exercise test; VE/VC02: ventilatory equivalent for carbon dioxide; EQ-5D-5L: EuroQol-5 Dimension- 5 Level; ALT: alanine transaminase; Cr: creatinine; BUN: blood urea nitrogen; Compound endpoint events: all-cause death, emergency/re-hospitalization for heart failure, acute coronary syndrome, revascularization, malignant arrhythmias, cardiogenic shock, stroke, pulmonary embolism, and so on.

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