Effects of Traditional Chinese Medicine Shensong Yangxin Capsules on Heart Rhythm and Function in Congestive Heart Failure Patients with Frequent Ventricular Premature Complexes: A Randomized, Double-blind, Multicenter Clinical Trial

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Abstract

Background: Pharmacological therapy for congestive heart failure (CHF) with ventricular arrhythmia is limited. In the study, our aim was to evaluate the effects of Chinese traditional medicine Shensong Yangxin capsules (SSYX) on heart rhythm and function in CHF patients with frequent ventricular premature complexes (VPCs).

Methods: This double-blind, placebo-controlled, multicenter study randomized 465 CHF patients with frequent VPCs to the SSYX (n = 232) and placebo groups (n = 233) for 12 weeks of treatment. The primary endpoint was the VPCs monitored by a 24-h ambulatory electrocardiogram. The secondary endpoints included the left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter, N-terminal pro-brain natriuretic peptide (NT-proBNP), New York Heart Association (NYHA) classification, 6-min walking distance (6MWD), Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores, and composite cardiac events (CCEs).

Results: The clinical characteristics were similar at baseline. SSYX caused a significantly greater decline in the total number of VPCs than the placebo did (−2145 ± 2848 vs. −841 ± 3411, $P < 0.05$). The secondary endpoints of the LVEF, NYHA classification, NT-proBNP, 6MWD, and MLHFQ scores showed a greater improvements in the SSYX group than in the placebo group (ΔLVEF at 12th week: 4.75 ± 7.13 vs. 3.30 ± 6.53; NYHA improvement rate at the 8th and 12th week: 32.6% vs. 21.8%, 40.5% vs. 25.7%; mean level of NT-proBNP in patients with NT-proBNP ≥125 pg/ml at 12th week: −122 [Q1, Q3: −524, 0] vs. −75 [Q1, Q3: −245, 0]; Δ6MWD at 12th week: 35.1 ± 38.6 vs. 17.2 ± 45.6; ΔMLHFQ at the 4th, 8th, and 12th week: −4.24 ± 6.15 vs. −2.31 ± 6.96, −8.19 ± 8.41 vs. −3.25 ± 9.40, −10.60 ± 9.41 vs. −4.83 ± 11.23, all $P < 0.05$). CCEs were not different between the groups during the study period.

Conclusions: In this 12-week pilot study, SSYX was demonstrated to have the benefits of VPCs suppression and cardiac function improvement with good compliance on a background of standard treatment for CHF.

Trial Registration: www.chictr.org.cn, ChiCTR-TRC-12002061 (http://www.chictr.org.cn/showproj.aspx?proj=7487) and Clinicaltrials.gov, NCT01612260 (https://clinicaltrials.gov/ct2/show/NCT01612260).

Key words: Congestive Heart Failure; Randomized Controlled Trial; Shensong Yangxin Capsules; Ventricular Premature Complexes

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Introduction

The presence of ventricular premature complexes (VPCs) in patients with congestive heart failure (CHF) was approximately 48% as monitored by the 24-h ambulatory electrocardiograms (ECGs).[1] VPCs generally causes

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dyssynchrony with reduced ventricular contraction, leading to adverse ventricular remodeling and is detrimental to ventricular systolic function.[2] Therefore, VPCs and CHF may provoke each other, creating a vicious cycle. In the past 2 decades, many attempts that were made to suppress symptomatic frequent VPCs with antiarrhythmic drugs (AADs) resulted in proarrhythmia, cardiac function inhibition, and a failure to improve survival. Therefore, pharmacological therapy is limited. Traditional Chinese medicine (TCM) has been developed more than 2000 years; over 70% patients in China preferred TCM combined with Western medicine.[3] Shensong Yangxin capsules (SSYX) is a combined herbal formulation widely used in China for the treatment of arrhythmia with or without structurally abnormal heart, which was approved by the China Food and Drug Administration in 2003. Based on the vessel-collateral theory of TCM, SSYX is extracted from 12 herb materials including *Ginseng*, *Ophiopogonis*, *Cornus officinalis*, *Salvia miltiorrhiza*, *Ziziphi spinosae semen*, *Taxilli herba*, *Paeoniae Radix Rubra*, *Eupolyphaga seu steleophaga*, *Nardostachyos*, *Coptis chinensis*, *Schisandrae sphenantherae fructus*, and *Os Draconis*. SSYX is now well known with the effects of modulatory of multiple ion current, ventricular remodeling, and autonomic nervous function.[4-10] Some single or multicenter clinical trials in China revealed that SSYX inhibits different types of arrhythmia as atrial fibrillation (AF) and VPC. Prescription of SSYX benefited the mild or moderate CHF patients with VPCs in clinical use, but it lacks scientific trials to evaluate the beneficial roles in CHF patients with symptomatic frequent VPCs. The purpose of this randomized, placebo-controlled study was to evaluate the clinical benefit of SSYX administration on VPCs and cardiac function in this commonly encountered clinical cardiology problem, which would provide a fundamental evidence for setting a more rigorous clinical trial to evaluate the long-term outcomes, including all-cause or cardiovascular mortality to validate whether the synergistic interactions of herbs in SSYX benefits the patients with CHF and VPCs as a result of a new treatment choice.

Methods

Ethical approval

The study protocol was reviewed and approved by the appropriate independent ethics committees. The research was conducted in accordance with the *Principles of Good Clinical Practice* and the *Declaration of Helsinki*. All eligible patients gave written informed consent.

Study setting and design

This study was designed as a multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical trial to assess whether SSYX administration can suppress VPCs as well as to improve cardiac function with good patient compliance. The trial was registered at ChiCTR-TRC-12002061 in Chinese Clinical Trial Registry and NCT01612260 in Clinicaltrials.gov.

The study was conducted at 30 clinical research centers throughout China from June 2012 to August 2014. The eligible patients, aged between 18 and 75 years, of both genders were enrolled in this trial based on the following four criteria: patients with documented CHF (Chinese guidelines published in 2007 for the diagnosis and management of CHF) who received optimal medical treatment with a stable maintenance dosage at least 3 months before the screening; the New York Heart Association (NYHA) classification on admission ranged between II and III, left ventricular ejection fraction (LVEF) ranged between 35% and 50% as calculated by the Simpson's formula with echocardiography; CHF was caused by ischemic heart disease or dilated cardiomyopathy; a total of symptomatic VPCs ranged between 720/24 h and 10,000/24 h according to a 24-h ambulatory ECG. Patients were excluded from the study if they met any one of the following conditions: CHF was caused by congenital heart disease, valvular disease, pericardial disease, or other noncardiogenic factors; the patient had unstable angina or acute myocardial infarction (MI), severe uncontrolled hypertension, left ventricular outflow obstruction, myocarditis, aneurysm, or cardiogenic shock; the patient had persistent AF, atrioventricular conduction block (Type II or III), sustained ventricular tachycardia (VT) or nonsustained VT associated with unstable hemodynamics, ventricular fibrillation, and sinus bradycardia less than 45 beats/min with pacemaker implantation; the patient had severe primary hepatic, renal, or hematologic disease; the patient had a severe mental health condition or other uncontrolled systemic disease; the patient had a serum creatinine level >194.5 mmol/L or serum potassium level >5.5 mmol/L; the patient had alanine aminotransferase or alkaline phosphatase levels >1.5 times the upper normal limit; the patient was pregnant or lactating; the patient was known or suspected to be allergic to the study drugs; the patient had received another investigational drug within 30 days before randomization; and the patient was unwilling or unable to provide written consent.

Treatment protocol and data collection

Patients enrolled in the study were randomly assigned into two groups who received SSYX or placebo treatment in addition to their usual care or prescribed medications for CHF. The dosage used in the research included four capsules/dose of SSYX or placebo three times daily for the entire 12-week duration of treatment. During the entire study period, any Class IA, IB, IC, III, and IV AADs or other traditional Chinese medicine were avoided; otherwise, the enroller would be withdrawn from the trial. Patients attended follow-up appointments at the 4th, 8th, and 12th weeks of treatment. At each visit, the symptoms were reviewed, the occurrence of any clinical event or adverse effect was documented, the vital signs were measured, and the dose of the study drug was recorded. The NYHA class was assessed, and Minnesota Living with Heart Failure Questionnaire (MLHFQ) was completed. A 24-h ambulatory ECG, echocardiography of LVEF,

left ventricular end-diastolic diameter (LVEDD), and 6-min walking distance (6MWD) test were performed at baseline and at the last visit. During the study period, routine laboratory assessments, such as chest radiography, complete blood count, urinalysis, and serum chemistry profile, were performed according to defined schedules at baseline and at the 12th week in the local laboratories of the participating institutions. The plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels at baseline and at the 12th week were measured with dedicated kit-based NT-proBNP assays (Roche Diagnostics, Basel, Switzerland) in the Department of Laboratory Medicine, Renmin Hospital of Wuhan University.

Study outcomes

The primary outcome of this study was the change of the total number of VPCs monitored by 24-h ambulatory ECG. The secondary outcomes included the changes of LVEF, LVEDD, plasma NT-proBNP level, NYHA classification, 6MWD, and MLHFQ scores.

Randomization and blinding

An independent company was contracted to pack the active drug SSYX and matching placebo as capsules in a 1:1 ratio with identical sizes and shapes. The participants, supervising doctors, and study nurses were not aware of the treatment allocation. Non-study personnel sealed, numbered, and sent the treatment packages to the study centers according to the computer-generated randomization code. On enrollment, patients accessed the treatment randomly by the assigned study identification number after signing the informed consent document. The randomization code could only be broken at the end of the study after the database was locked. In an emergency, due to clinical need, the date and reason for breaking the code would be recorded in the case report form.

Sample size and statistical analysis

We estimated that a total of 378 patients in the SSYX and placebo groups would need to be enrolled to provide the study with a statistical power of 90% for detecting a 25% difference in the mean reduction percent of the total number of VPCs monitored with a 24-h ambulatory ECG at week 12 and a two-sided significance level of 0.05, assuming a 45% of the mean reduction in the SSYX group and a 20% mean reduction in the placebo group. However, considering a possible 20% dropout rate, we planned to include 460 patients (230 per group) in this study.

Analysis of the primary outcome was conducted by Student's *t*-test according to the intention to treat in the population with all randomized patients receiving at least one dose of treatment in each group at week 12. Analysis of the secondary outcomes, including LVEF, LVEDD, plasma NT-proBNP level, NYHA classification, 6MWD, and MLHFQ scores, was performed using Student's *t*-test at week 12. The NT-proBNP is presented as the median and interquartile range due to the skewed distribution. The NYHA functional classification, composite cardiac events (CCEs), and proportions of NT-proBNP reduction ≥30% were analyzed by Chi-square or Fisher's exact test at weeks 4, 8, and 12. The safety analysis was based on the account and incidence of adverse events in the evaluable-for-safety population, consisting of those patients who had received study medication and who had at least one postbaseline safety evaluation. The incidences were analyzed by Chi-square or Fisher's exact test.

Continuous variables are presented as the mean ± standard deviation (SD) or median (Q1, Q3), and categorical variables are presented as the total number and percentages. All statistical analyses were performed with the SAS statistical software package (version 9.1.3, SAS Institute, Cary, North Carolina, USA). All statistical tests were two-sided with a significance level of 0.05.

Results

Between June 2012 and August 2014, a total of 465 patients were enrolled and randomized to the SSYX (n = 232) and placebo groups (n = 233) during the study. Fifty-four patients enrolled withdrew consent with which the major reasons were adverse effects (7 in SSYX group and 13 in placebo group); lost to follow-up (15 in each group); and four patients in placebo groups with the problem of noncompliance with protocol (n = 2) and other reasons (n = 2). An overview of the study population is shown in Figure 1. Baseline characteristics of the study population are presented in Table 1. There were no statistically significant differences between the two groups for the demographic, clinical, and cardiac characteristics or medication.

The changes of VPCs in a 24-h ambulatory ECG were observed at baseline and after 12 weeks of treatment; the parameters are summarized in Table 2. Compared with the placebo group, the total number of VPCs in 24 h at the week 12 visit was significantly lower in the SSYX group (1538 ± 2187 vs. 2746 ± 3889, $P < 0.05$) and the mean reduction value of VPCs was much higher in the SSYX group (ΔVPCs −2145 ± 2848 vs. −841 ± 3411, $P < 0.05$). Calculated with the formula (week 12 value − baseline value)/baseline value, the SSYX group had a higher reduction rate at −0.51 ± 0.59 versus −0.22 ± 0.82 in the placebo group ($P < 0.05$). To evaluate the favorable effects of SSYX administration with a powerful method, the patients at four different VPCs reduction percentage levels were analyzed. According to Table 2, the number of patients at reduction percentages of 90%, 70%, 50%, and 30% was significantly higher in the SSYX group than in the placebo group ($P < 0.05$).

Figure 2 summarizes the results of the echocardiogram analysis. At baseline, patients in the two groups demonstrated no significant difference in the LVEF and LVEDD. At the 12 weeks visit, the SSYX group had more improvement in cardiac function with a higher mean change in LVEF (ΔLVEF 4.75 ± 7.13 vs. 3.30 ± 6.53, $P < 0.05$) as compared with the placebo group. However, there was no significant decrease in the LVEDD in both groups.

After 12 weeks of treatment, the plasma NT-proBNP changed in both groups showed a significant decrease in the

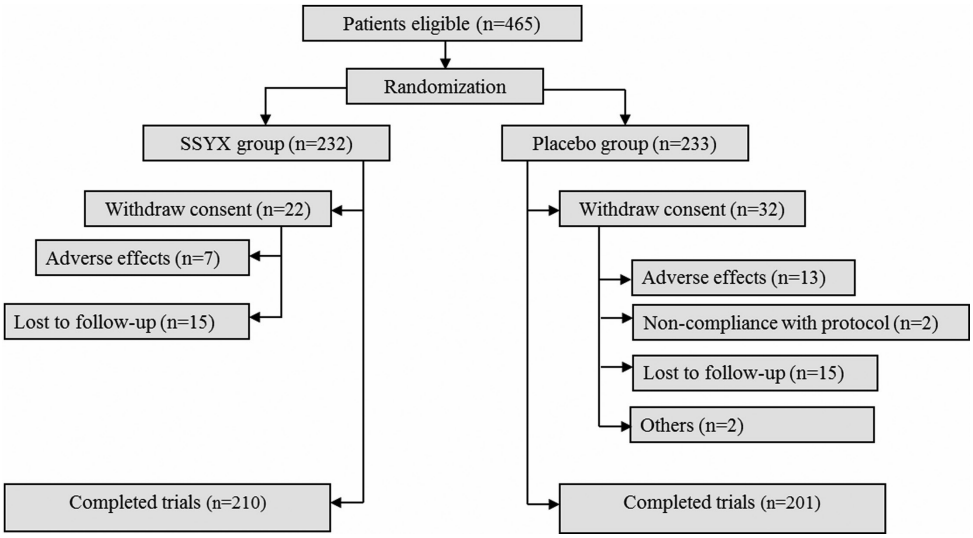

Figure 1: Overview of the study population. SSYX: Shensong Yangxin capsules.

Table 1: Baseline characteristics of the patients

Characteristics	SSYX (n = 210)	Placebo (n = 201)	Statistic value	P
Demographics				
Age (years)	60.4 ± 10.8	59.8 ± 10.9	0.594*	0.553
Male, n (%)	139 (59.9)	153 (65.7)	1.646*	0.200
Ethnicity, n (%)				
Han	224 (96.6)	224 (96.1)	0.057†	0.812
Other	8 (3.4)	9 (3.9)		
Heart rate (beats/min)	74.1 ± 8.9	73.3 ± 9.7	0.912*	0.362
Systolic pressure (mmHg)	126 ± 13	127 ± 13	0.922*	0.357
Diastolic pressure (mmHg)	77.8 ± 9.0	77.7 ± 9.4	0.110*	0.913
Medication, n (%)				
ACEI	125 (53.9)	122 (52.4)	0.108†	0.743
ARB	88 (37.9)	85 (36.5)	0.105†	0.746
Beta-blocker	185 (79.7)	190 (81.5)	0.242†	0.623
Aldosterone antagonists	151 (65.1)	142 (60.9)	0.856†	0.355
Diuretics	144 (62.1)	152 (65.2)	0.504†	0.478
Digoxin	65 (28.0)	61 (26.2)	0.199†	0.656
NYHA Class, n (%)				
II	166 (71.6)	167 (71.7)	0.001†	0.977
III	66 (28.4)	66 (28.3)		
Echocardiography parameters				
LVEF (%)	43.5 ± 5.4	43.4 ± 5.2	0.135*	0.892
LVEDD (mm)	56.9 ± 10.5	57.1 ± 10.1	0.251*	0.802
Plasma NT-proBNP (pg/ml)	399 (144, 1705)	418 (147, 1346)	0.235‡	0.628
6MWD (m)	351 ± 97	368 ± 89	1.304*	0.194
MLHFQ	30.1 ± 15.3	28.8 ± 15.4	0.930*	0.353
24-h ambulatory ECG				
Total VPCs (beats/24 h)	3683 ± 2895	3587 ± 2741	0.368*	0.713
Total heartbeat (beats/24 h)	101,034 ± 14,499	103,168 ± 15,386	1.539*	0.125
Mean heartbeat (beats/min)	71.7 ± 9.7	72.4 ± 10.6	0.706*	0.480

Values are given as the mean ± SD, n (%), or median (Q1, Q3). 1 mmHg = 0.133 kPa. *: t test, †: Chi-square test, ‡:Wilcoxon test. SSYX: Shensong Yangxin capsules; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; NYHA: New York Heart Association; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; NT-proBNP: N-terminal pro-brain natriuretic peptide; 6MWD: 6-min walking distance; MLHFQ: Minnesota Living with Heart Failure Questionnaire; VPCs: Ventricular premature complexes; SD: Standard deviation; ECG: Electrocardiogram.

NT-proBNP level, which were 208 (Q1, Q3: 56, 839) versus 399 (Q1, Q3: 144, 1705) in the SSYX group ($P < 0.05$) and 287 (Q1, Q3: 67, 1182) versus 418 (Q1, Q3: 147, 1346) in the placebo group ($P < 0.05$). Because there is a consensus on

Table 2: 24-h ambulatory electrocardiogram data of the patients

24-h ambulatory ECG	SSYX (n = 210)	Placebo (n = 201)	Statistic value	P
Total VPCs, beats/24 h				
Baseline	3683 ± 2895	3587 ± 2741	0.368*	0.713
Week 12	1538 ± 2187	2746 ± 3889	4.131*	<0.001
Week 12 − baseline	−2145 ± 2848	−841 ± 3411	4.477*	<0.001
Reduction rate of total VPCs (%)	−51 ± 59	−22 ± 82	4.321*	<0.001
Patients with a VPC reduction percentage, n (%)				
90% of reduction	77 (33.2)	50 (21.5)	15.958†	0.005
70% of reduction	117 (50.4)	75 (32.2)	13.970†	<0.001
50% of reduction	152 (65.5)	101 (43.3)	23.033†	<0.001
30% of reduction	166 (71.6)	125 (53.6)	15.912†	<0.001

Values are given as the mean ± SD or n (%). *: t test, †: Chi-square test. SSYX: Shensong Yangxin capsules; SD: Standard deviation; ECG: Electrocardiogram; VPCs: Ventricular premature complexes; reduction rate of total VPCs = (week 12 value − baseline value)/baseline value.

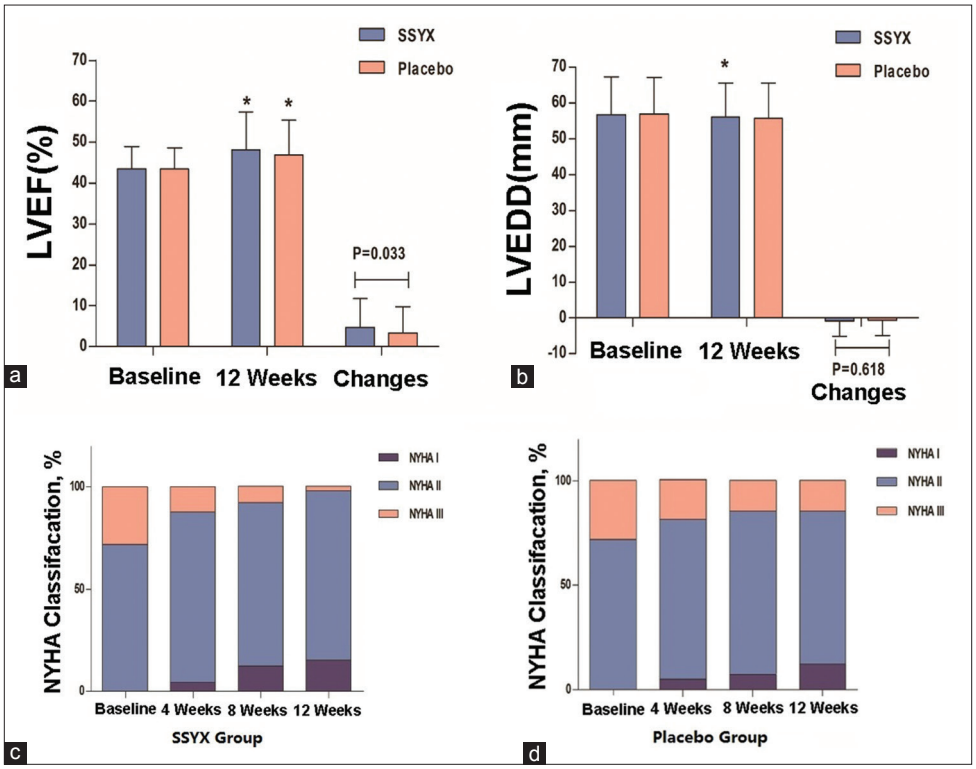

Figure 2: Echocardiography measurement assessment of the left ventricular function and NYHA classification. LVEF (a) and LVEDD (b) are depicted at baseline and 12 weeks treatment. NYHA functional classification shown are the relative proportion of patients in SSYX group (c) and placebo group (d) with NYHA Class I to II versus III to IV symptoms at baseline, 4 weeks, 8 weeks, and 12 weeks of treatment. *P < 0.05 versus baseline. SSYX: Shensong Yangxin capsules; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; NYHA: New York Heart Association.

the accuracy of NT-proBNP for heart failure (HF) at a cutoff value of 125 pg/ml, the subgroup analysis was performed in the patients with NT-proBNP ≥125 pg/ml before and after the treatment. There were 174 patients in the SSYX group and 177 patients in the placebo group with no difference in the value of NT-proBNP at baseline; 12 weeks of SSYX treatment resulted in a significant larger reduction in NT-proBNP as compared to the placebo (−122 [Q1, Q3: −524, 0] vs. −75 [Q1, Q3: −245, 0], P < 0.05).

The NYHA class was evaluated at baseline and each visit of the 4th, 8th, and 12th weeks of treatment. The following three categories were used to assess changes in the symptoms of HF: improvement, no change, and deterioration. Improvement was defined as the NYHA class improving at least one grade, and deterioration was defined as the NYHA class worsening at least one grade. As shown in Figure 2, there were no significant differences in the NYHA functional class between the two groups at baseline and at the 4th week visit. At the 8th and 12th week visits, the percentage of patients in NYHA Classes I, II, and III was significantly different in the two groups; the SSYX group had superior improvements, with improvement percentages of 32.6% and 40.5% in the SSYX group versus 21.8% and 25.7% in placebo group (P < 0.05, respectively).

The 6MWD test was performed at baseline and at the 12th week visit. There was no difference between the two groups at baseline; compared with the placebo group, patients receiving SSYX treatment had a greater increase in the 6MWD at week 12 (Δ6MWD 35.1 ± 38.6 vs. 17.2 ± 45.6, $P < 0.05$).

The MLHFQ was completed at each visit. There was a gradual improvement in the quality of life during the entire treatment period, and SSYX compared to placebo resulted in greater changes in the scores at the 4th, 8th, and 12th week visits (ΔMLHFQ −4.24 ± 6.15 vs. −2.31 ± 6.96, −8.19 ± 8.41 vs. −3.25 ± 9.40, −10.60 ± 9.41 vs. −4.83 ± 11.23, all $P < 0.05$).

The assessments of safety and tolerability were based on spontaneous reports of adverse events, vital signs, and laboratory measurements. CCEs were defined as death, cardiac arrest with resuscitation, readmission for HF, worsening HF with an intravenous pharmacological agent for more than 4 h, stroke or cases in which the patient ceased active treatments because of worsening HF. Overall, 2.2% and 3.5% of patients in the SSYX and placebo groups experienced CCEs ($P = 0.403$). One patient died and four patients were readmitted to the hospital for HF in the SSYX group. In the placebo group, one patient died, six patients were readmitted to the hospital for HF, and one patient received implantable cardioverter defibrillator treatment for worsening HF. The total number of adverse events was 39 in the SSYX group versus 52 in the placebo group ($P = 0.134$). The analysis of drug-induced adverse events revealed no differences between the two groups. There was no report of any serious adverse events related to the study drugs.

Discussion

In the present study of CHF patients with frequent VPCs, we demonstrated that, combination with usual care and therapy for CHF, 12 weeks of SSYX treatment had more significant suppression of VPCs and improvement of cardiac function. These results suggest that SSYX might benefit CHF patients by improving ventricular electrostability and reversing ventricular remodeling.

Frequent VPCs are commonly encountered in patients with CHF, and they always produce a less efficient ventricular contraction in aggravating ventricular dysfunction. On the other hand, as the cardiac function worsens, the frequency of VPCs and complexity of ventricular dysrhythmias increase.[11-14] Therefore, the therapy that is given to break the vicious cycle is considered to be crucial. VPCs provide an arrhythmogenic substrate with a ventricular electrical instability that is the potential cause of malignant arrhythmia and cardiovascular mortality.[15] Therefore, many studies have been conducted to suppress frequent VPCs by either AADs or catheter ablation. Unfortunately, in spite of substantial effort focusing on drug development, few AADs are available for clinical use because the benefits of VPCs suppression in CHF patients are usually counteracted by the negative inotropic and proarrhythmic effects of AADs, which also failed to improve survival. At present, among the Class IA, IB, IC, II, III, and IV AADs, only amiodarone seems to improve the ventricular function as well as has an antiarrhythmic effect in CHF patients with VPCs without increasing the mortality rate.[16,17] However, the extracardiac side effects of amiodarone, including effects on the thyroid, lungs, and liver, have hampered its clinical utility. β-blockers are a cornerstone of pharmacotherapy for CHF; however, the VPCs response to β-blockers changes to a variable extent, and they are rarely completely suppressed in CHF patients.[18-21] Therefore, the pharmacological treatment options in CHF patients with frequent VPCs are limited.

The recorded description that palpitation was diagnosed as symptomatic premature beats around 600 BC with pulse palpation from the early Chinese physicians.[22] Chinese medicinal herbs have been used over the past centuries in China for treating arrhythmia and increased in popularity as complementary and alternative therapeutic agents used worldwide. However, few have been subjected to the rigorous evaluation processes. SSYX is a well-known compound with antiarrhythmic effects described in the *Chinese Materia Medica* textbook.[23] According to the method of ultra-fast liquid chromatography combined with quadrupole time-of-flight mass spectrometry, the 12 herb materials of SSYX that were definitely identified or tentatively characterized could be classified into seven fractions, including saponins, phenolic acids, tanshinones, lignans, terpenoids, alkaloids, and flavonoids. The characteristic behaviors were investigated, and 11 representative compounds were found.[24,25] Previous pharmacological studies revealed that SSYX suppresses arrhythmias that are induced by toxic chemical compounds or ischemia-reperfusion injury in animal models.[26,27] SSYX was found to block multiple ion channels in isolated ventricular myocytes, inhibiting the sodium current, L-type calcium current, transient outward potassium current, delayed rectifier current, and inward rectifier potassium current.[5] In a randomized, double-blind, controlled multicenter trial conducted in patients with or without organic heart disease, SSYX compared with placebo or mexiletine had a significant therapeutic efficacy in reducing VPCs and alleviating VPCs-related symptoms.[28] Another randomized controlled trial of SSYX combined with routine pharmacotherapy in chronic HF revealed that SSYX further normalizes the heart rate variability (HRV) and heart rate turbulence (HRT) as well as reduces the incidences of VT and AF compared with the routine pharmacotherapy for HF alone.[29]

In our study, SSYX showed antiarrhythmic effects that were similar to those in basic and clinical studies, leading to a significant decrease in the total number of VPCs and demonstrating a greater reduction compared to placebo. On the other hand, the proarrhythmic effects of SSYX were assessed by a comparison of variety of complexity in VPCs and total arrhythmia. SSYX had a downward trend in

monomorphic, polymorphic, multifocal, paired, bigeminy, or trigeminy VPCs and in NSVT. Neither severe arrhythmia nor malignant arrhythmia was observed in the 24-h ambulatory ECG. We found that SSYX-mediated suppression of the frequency VPCs resulted in an improvement in the cardiac function. SSYX treatment improved the NYHA classification and increased the LVEF. SSYX also helped reduce the plasma NT-proBNP and enhance the 6MWD and quality of life. All of the data showed that SSYX performs better than placebo. Previous studies have reported that eliminating VPCs with catheter ablation or suppressing VPCs with amiodarone improves or normalizes the ventricular function.[16,30-32] Therefore, suppressing VPCs by SSYX led to a benign effect on cardiac function. However, in addition, we speculated that the SSYX-mediated cardiac function improvements were not only due to inhibition of VPCs but also from other underlying regulatory mechanisms. More recently, basic and clinical studies have reported that SSYX provides some regulatory effects on the intermediate interaction between the mechanical and electrical function of the heart. In our rabbit models of MI or HF, 8 weeks of treatment with SSYX powder revealed that SSYX could reverse electrical remodeling with a shortening action potential duration and transmural dispersion of repolarization.[7] In a diabetes rat model, 4 weeks of SSYX administration markedly improved the impaired cardiac function and attenuated the cardiac fibrosis and collagen deposition with the suppression of transforming growth factor-β1/Smad signaling pathway.[8,9] An MI rabbits' research found that SSYX inhibited ventricular neural remodeling by reducing the densities of growth associated protein 43 and tyrosine hydroxylase positive nerve fibers.[10] Another study in the paroxysmal AF canine model revealed that SSYX has association with regulating the imbalance of autonomic nerve activity.[33] As mentioned previously, SSYX normalized the HRV and HRT in a chronic HF clinical trial, suggesting that SSYX treatment might rebuild the balance of the autonomic nervous system. The results from the basic and clinical research data suggest that SSYX might modulate the neurohormonal, structural, and functional remodeling to improve cardiac function, except for enhancing myocardial electrical stability.

Although the exactly active ingredients and the clearly mechanism of SSYX on VPCs and CHF remain unknown, some researches of part of the compositions involved in SSYX may explain part of the underlying pharmacodynamic profiles. *Ginseng*, the emperor herb in SSYX, has been revealed a number of beneficial properties in cardiac protection as protecting the ischemia-reperfusion injury, attenuating myocardial hypertrophy, and blunting the remodeling and HF processes.[34] Tanshinones from the *S. miltiorrhiza* in SSYX were demonstrated to suppress ischemic arrhythmias as well as prevent cardiac injury, hypertrophy, and atherogenesis. Downregulation of miR-1 and consequent recovery of Kir2.1, activation of KCNQ1/KCNE1 potassium channels may account partially for the efficacy of tanshinone IIA in arrhythmia suppression.[35-37] Since SSYX is a complicated herbal composition, larger validation studies are needed to provide further evidence for its active ingredients and mechanisms.

Study limitations

In our study, 24-h ECG was used to evaluate the situation of VPCs. However, the frequency of VPCs is also subjected to daily or periodic variations, so prolonged period up to 72 h or even 7 days ECG is proposed to be more convincing. Since 12-week period in our study is a short time point, a larger scale and a longer term as 12 months of a rigorous designed clinical trial should be carried out for a more comprehensive analysis of SSYX in CHF patients with VPCs.

Conclusions

On a background of routine pharmacotherapy in CHF patients with frequent VPCs, SSYX treatment showed more significant VPCs suppression and further cardiac functional improvement. The bidirectional benefits of the mutual promotion of SSYX in mechanical and electrical functions are derived from the comprehensive modulations of neurohormonal, structural, and electrical remodeling. A rigorous clinical trial that evaluates the long-term outcomes, including all-cause or cardiovascular mortality, is needed to validate that SSYX provides clinical benefits to CHF patients with frequent VPCs following this study.

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Conflicts of interest

Shijiazhuang Yiling Pharmaceutical Co., Ltd., (Shijiazhuang, China) provided the Shensong Yangxin capsules.

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