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Shen'ge Formula Could Protect Heart Function: A Traditional Chinese Medicine Method for Heart Failure

Boyong Qiu[1], Wang Zheng[2], Suyun Yuan[2], Lin Shen[2], Duan Zhou[2], Shaofeng Wang[3, *], Yihong Wei[2, *]

[1]The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou, China

[2]Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China

[3]Chuansha Huaxia Community Health Service Center, Shanghai, China

Email address:

13801905528@139.com (Shaofeng Wang), tcmwyhdoc@163.com (Yihong Wei)

[*]Corresponding author

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Abstract: Heart failure (HF) is a worldwide health issue, and the application of Chinese medicine could provide new methods for the treatment of HF. Currently, there is no good medicine for diastolic heart failure (DHF) at present; therefore, we hope our study can confirm the effectiveness of Shen'ge formula (SGF) in the treatment of DHF and provide new strategies for patients with HF. To analyze the potential effect of SGF against HF, especially against DHF, we consult and summarize our previous researches on SGF. Our previous clinical studies demonstrated that SGF combined with conventional western medicine was able to improve ventricular contractility, heart function and reduce serum brain natriuretic peptide (BNP)/NT-proBNP levels of patients. The quality of life and clinical symptoms in HF patients were significantly improved after intervention. And basic researches also manifested that SGF was capable of preserving heart function, improving symptoms, and reducing cardiac hypertrophy and fibrosis in rats. Mechanisms involved in SGF ameliorating heart function probably were through downregulating AT1R, NADPH oxidase 2, 4, inhibiting TGF-β/smads pathway and RhoA/ROCK1 pathway. And SGF reducing serum metabolites accumulation was feasibly by up-regulating heart mRNA expressions of COX2, ATP6 and ATP8. In all, SGF exhibits many advantages in HF treatment according to the results of our previous researches, which indicates that SGF could be the potential beneficial strategy in DHF.

Keywords: Heart Function, Heart Failure, Shen'ge Formula, Traditional Chinese Medicine

1. Introduction

Shen'ge formula (SGF) has been used clinically for thousands of years, of which the record can be traced back to the Song Dynasty of China's Medical books named ShengJiZongLu. SGF, which is composed of ginseng and gecko, nourishes the lungs and kidneys, absorbs qi, and relieves asthma. The original text contains the treatment of lung qi cough, facial swelling, and limb edema; in clinical use for asthma, edema, and other symptoms of treatment. These symptoms are consistent with the symptoms of heart failure (HF) in modern medicine. According to the theory of Chinese medicine, we applied SGF to the treatment of HF.

HF is a chronic disease caused by a decline in heart function, such as shortness of breath, edema and other clinical symptoms. As the advanced stage of various heart diseases, the mortality and rehospitalization rates of HF remain high. The annual incidence of HF worldwide is approximately 100~900 cases per 100,000 people [1]. In developed countries, the prevalence of HF is approximately 1.5%-2.0%, and the incidence in people over 70 years of age is more than 1/10 [2]. The epidemiological survey in 2012-2015 showed that the prevalence rate of HF in China was continued to increase, while the rate of HF in residents aged ≥35 years was 1.3%, with a patient population of 13.7 million [3]. The length of stay in patients with HF was

approximately 10 days and the mortality rate was approximately 4.1% [4].

HF can be divided into HF with decreased ejection fraction (HFrEF), HF with mid-range ejection fraction and HF with preserved ejection fraction (HFpEF) [5]. HFpEF, also known as diastolic HF (DHF), is an important type of HF. The PARADIGM-HF 2015 study showed that sacubitril/valsartan could reduce hospitalization and cardiovascular mortality in patients with HFrEF by approximately 20% and all-cause mortality by about 16% [6]. However, the study of PARAGON-HF 2019 demonstrated that sacubitril/valsartan failed to reduce hospitalization and cardiovascular mortality in patients with DHF [7]. To date, there has been no breakthrough in drug treatment research for DHF. Hence, HF, especially DHF, remains an important concern, which is accessed and discussed in further study.

2. Animal Study

2.1. SGF Improved Heart Function

Abdominal aortic constriction (AAC) could increase peripheral circulation resistance, reduce ejection fraction (EF), cause wall thickening and cardiomyocyte hypertrophy, and affect cardiac systolic and diastolic function [8, 9]. Both abdominal aortic coarctation and thoracic aortic coarctation could reduce cardiac pump function in rats. In comparison, the survival rate of AAC is relatively high, the effect of HF is accurate and the repeatability is high, which is widely used by experimental researchers [10, 11].

In previous studies, we established a rat model of pressure overload HF by AAC to explore the cardioprotective effect of SGF. We found that SGF could improve hemodynamic force and cardiac hyperintensities in rats with pressure overload HF. The results showed that, after the intragastric administration of SGF for 8 weeks [12, 13], the SGF group experienced a significant improvement in the EF, left ventricular systolic pressure, maximum rate of pressure rise in the left chamber (+dp/dt max), decreased left ventricular systolic diameter, and maximum rate of pressure drop in the left chamber (-dp/dt max) compared with the AAC model. Similarly, after intragastric administration for 12 weeks [14], we found that SGF was good for the EF and ±dp/dt max of rats, and SGF decreased left ventricular end-diastolic pressure and reduced myocardial tissue lesions and myocardial fibrosis. Furthermore, in a 16 weeks gavage of SGF [15], the results showed that the left ventricular systolic and diastolic functions of HF rats were all improved by SGF. In summary, SGF can improve heart function in rats at different stages of HF by improving cardiac compliance, increasing EF, and inhibiting ventricular remodeling.

2.2. SGF Ameliorated Cardiac Hypertrophy and Myocardial Fibrosis

Myocardial hypertrophy is an important pathological process in patients with HF. The loss of elasticity of myocardial fiber tissue leads to a decrease in ventricular filling, which is due to decreased ventricular compliance and eventually impaired ventricular contraction. This leads to increased left ventricular systole load exacerbation and hypertrophy [16]. The initial stage of cardiac hypertrophy is an adaptation to physiological or pathological stimuli, and pathological hypertrophy generally progresses to a decrease in cardiac output and symptoms of HF [17]. Cardiovascular risk is high in patients with cardiac hypertrophy, and hypertrophy can lead to increased fibrosis, insufficient blood vessel growth, and impaired cardiac function [18]. These pathological changes accelerate the process of HF.

In addition to myocardial hypertrophy, myocardial fibrosis is an important pathological process in HF. Ventricular remodeling involves all cells throughout the heart, including cardiomyocytes, fibroblasts, and endothelial cells. Under the action of pathological factors, the heart showed fibroblast proliferation, accumulation of proinflammatory mediators, and fibrosis-induced extracellular matrix recombination [19]. Accompanied by the accumulation of interstitial collagen fibers, capillary density decreases and oxygen diffusion distance increases, leading to hypoxia and dysfunction of cardiomyocytes and decreased contractility and compliance of the myocardium, resulting in ventricular systolic and/or diastolic dysfunction [20].

Myocardial hypertrophy and fibrosis increase the burden of the heart pump function. As the burden gradually worsen, patients experience chest tightness, asthma and other clinical symptoms [21] or even arrhythmias [22]. In our study, cardiac ultrasound and hematoxylin and eosin staining were also performed in HF rats. The results showed that myocardial hypertrophy and myocardial fibrosis were very apparent in the AAC group, while in the SGF group, the left ventricular mass index [15], myocardial hypertrophy, and myocardial fibrosis was significantly reduced in rats with HF [13, 14]. These results suggest that SGF inhibits myocardial hypertrophy and fibrosis.

2.3. Mechanism Study on SGF

Our investigations revealed the mechanism of SGF in the protection of cardiac function. After 5 weeks of gavage, we observed the effect of SGF on the AT1R of myocardial tissue in rats with pressure overload HF ventricular remodeling, and the results showed that SGF significantly decreased AT1R and cardiac index [23]. SGF can downregulate the mRNA expression of myocardial TGF-β1 and Smad3 and upregulate the expression of Smad7, and the protein expression of TGF-β1 and Smad3 were also inhibited by SGF [24]. In addition, a research verified that SGF could inhibit the expression of RhoA, ROCK1 [12], and NADPH oxidase 2,4 [25] in cardiomyocytes in rats with pressure overload. We found that in mitochondrial pathway studies, SGF might protect myocardial mitochondria by upregulating the expression of cardiac COX2, ATP6, and ATP8 and reducing the accumulation of serum metabolites [26]. We have thoroughly analyzed the mechanisms of the SGF, but the complete mechanism of SGF has not been fully elucidated and needs further exploration.

3. Clinical Study

We conducted two clinical studies on the treatment of HF with SGF. We performed 8 weeks of clinical intervention in our first study. In this study, 60 patients with HF were randomly divided into two groups: control group was treated with conventional western therapy, and treatment group received conventional therapy combined with SGF. At baseline and 8 weeks after treatment, the level of BNP in serum, score of TCM syndrome, and left ventricular ejection fraction (LVEF), stroke volume (SV), CO and E/A were detected. And the results showed that the total effective rate of cardiac function in the treatment group and the control group were 86.67% and 46.67% respectively, with a difference between them (P<0.01). After treatment, the scores of TCM syndrome and the levels of BNP in two groups were significantly decreased (P<0.05, P<0.01), with better results in the treatment group than in the control group (P<0.01). After treatment, the levels of LVEF, SV and CO were all improved in both groups (P<0.05); LVEF, SV, CO and E/A value in the treatment group were more significantly improved than those in the control group (P<0.05, P<0.01). The results demonstrated that SGF in combination with Western medicine worked better than Western medicine alone. In this experiment, SGF could also improve the symptoms and reduce the serum brain natriuretic peptide (BNP) levels of patients [27].

Furthermore, we conducted a 12-week clinical study. A total of 72 cases were collected and randomly divided into a treatment group and a control group with 36 cases in each group. The control group was given conventional western medicine, while the treatment group was given SGF in addition to western medicine. The course of the treatment was 12 weeks. The heart function level, TCM syndrome score, 6 minutes walking test (6MWT), Lee's heart failure score and Minnesota Living with Heart Failure Questionnaire (MLHFQ) were evaluated before and after treatment, LVEF, SV, serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) level were determined. Results showed that the total effective rates of heart function, TCM syndrome, Lee's heart failure score of patients in the treatment group were 94.4%, 97.2%, and 94.4%, respectively, while those of the control group were 72.2%, 66.7%, and 77.8% respectively. The treatment group was significantly superior to the control group (P<0. 05). After treatment, the MLHFQ score and serum NT-proBNP level of both groups were significantly lower than those before treatment (P<0.05 or P<0.01), and the 6MWT, LVEF value and SV level were significantly higher than those before treatment (P<0.05 or P<0.01). Compared with the control group, the MLHFQ score and serum NT-proBNP level of the treatment group were significantly lower, and the 6MWT, LVEF and SV levels were higher (P<0.05 or P<0.01). The results confirmed that SGF, in combination with basic Western medicine, significantly decreased the score of MLHFQ and the serum level of NT-proBNP, and increased 6-minute walking distance, LVEF, and SV in patients with HF [28].

The two experiments show that SGF can effectively improve the indicators of patients with HF, including improving cardiac function and clinical symptoms. To better use SGF in the treatment of HF, we are now conducting a randomized, double-blind, placebo-controlled clinical study to comprehensively evaluate the clinical efficacy and safety of SGF in the treatment of DHF [29]. There is no definite clinical drug for DHF, and the results of the PARAGON-HF 2019 study for DHF are negative [7]. Therefore, we hope that we can find ways to provide more and better treatments for DHF. DHF is an important pathological type of heart failure, that involves multiple organ dysfunction and multiple complications. This randomized, double-blind, placebo-controlled clinical trial will evaluate the efficacy and safety of SGF in the treatment of DHF. A total of 130 patients with DHF will be enrolled in the trial and treated with SGF granules or placebo for 12 weeks and followed up for 12 weeks. The primary outcome measurement will be to changes in plasma NT-proBNP before versus after treatment, while the second primary outcome measurement will be changes in heart function before versus after treatment and the 12-week follow-up period. It will also include echocardiography, a cardiopulmonary exercise test, cardiac function grading, TCM syndrome score, and the MLHFQ. Adverse events will be evaluated throughout the trial. The results of this trial will demonstrate whether SGF could alleviate symptoms, improve cardiac function, reduce readmission rates, and improve quality of life of patients with DHF.

4. Summary

DHF is the focus and difficulty of cardiovascular research, which requires further exploration. Chinese herbal medicine can improve the symptoms of patients with HF and improve their quality of life [30, 31]. In Asia, it has been used for treating heart disease for thousands of years, but there is a lack of evidence-based medical data. Many experimental and clinical studies in the early stages have shown that SGF can alleviate the typical symptoms of patients with HF, improve heart function, and inhibit myocardial hypertrophy and fibrosis from inhibiting ventricular remodeling. This indicates the potential of SGF in the treatment of DHF. Our recent clinical study will scientifically evaluate the clinical application of SGF in DHF and provide objective, true, and evidence-based consequences, which might provide new feasible means and ideas for the treatment of DHF with traditional Chinese medicine. This might also contribute to the application to traditional Chinese medicine to aid the development of human medicine.

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