

# Progress in the Application of Traditional Chinese Medicine in the Treatment of Heart Failure with Preserved Ejection Fraction

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**Abstract:** Heart failure with preserved ejection fraction has attracted more and more attention in recent years because its mechanism is different from heart failure with reduced ejection fraction, and accounts for a high proportion of heart failure. At present, there are only sodium-glucose cotransporter 2 inhibitors for their IA drugs in the guidelines. The advantages of traditional Chinese medicine in treating heart failure lies in This article reviews the research related to the intervention of traditional Chinese medicine in HFpEF with a view to clarifying the long-term efficacy of traditional Chinese medicine in treating HFpEF.

**Keywords:** Traditional Chinese medicine, Ejection fraction, Heart failure, Application progress.

## 1. Introduction

Heart failure is a group of complex clinical syndromes caused by multiple causes of abnormal changes in heart results and/or function, causing ventricular contraction and/or diastolic dysfunction [1]. Heart failure with preserved ejection fraction (HFpEF) is a special type of heart failure. The patient's left ventricular ejection fraction (LVEF) is  $>50\%$ . The heart can pump blood normally or basically normally when contracting, but it still shows symptoms of heart failure, and the symptoms gradually worsen over time [2]. Studies have shown that the incidence of HFpEF is increasing, accounting for about 50% of all heart failure patients, and the fatality rate and re-hospitalization rate are not significantly lower than heart failure with reduced ejection fraction (HFrEF) [3]. At present, the clinical treatment principle of HFpEF is to improve the diastolic function of the heart and improve ventricular conformity, thus reducing the burden on the heart. Western medicine treatment of HFpEF is mostly drug treatment, but the effect of conventional Western medicine for the treatment of heart failure needs to be improved in improving the prognosis of patients. The treatment principle of traditional Chinese medicine of "prevent disease before disease, prevent disease" is in line with the concept of preventing and delaying the occurrence of heart failure pointed out in the guidelines of the European Cardiology Society in 2021 [4]. Traditional Chinese medicine treatment of heart failure has the advantages of multi-path, multi-target and multi-mode. In recent years, the research on HFpEF-related traditional Chinese medicine has gradually increased. Under the guidance of the overall concept and dialectical treatment of traditional Chinese medicine theory, this article reviews the relevant research on the treatment of HFpEF in traditional Chinese medicine.

## 2. The Traditional Chinese Medicine's Understanding of HFpEF

### 2.1 Traditional Chinese Medicine's Understanding of HFpEF Disease Names

The symptoms of heart failure with different ejection fractions

are similar, mainly manifested as dyspnea, edema and decreased exercise endurance. According to the clinical manifestations, traditional Chinese medicine classifies it into the category of palpitations, edema, asthma, heart water and so on [5]. The "Huang Di Nei Jing" records: "People can't lie flat. Once they lie flat, they will cause cough and asthma, mainly due to edema caused by water retention". It points out the characteristics of the disease that the disease cannot lie flat. The pathone is "edema caused by water retention". The "Jin Gui Yao Lue" points out: "Person is heavy and less qi, he can't lie down, he is annoying and dry, and his person is yin and swollen". The symptoms such as edema, irritability, and not lying flat are basically the same as heart failure. The discussions such as "water retention in the heart, even palpitations, and shortness in small ones" are in line with the symptoms of HFpEF in modern medicine.

### 2.2 Understanding of the Etiology and Pathogenesis of HFpEF in Traditional Chinese Medicine

In the theory of traditional Chinese medicine, the etiology and pathogenesis of HFpEF are closely related to long-term qi and blood, visceral dysfunction and yin-yang imbalances [7]. Traditional Chinese medicine believes that qi is the most basic substance that constitutes the body and maintains the life activities of the body. Blood is mainly composed of water grain essence and kidney refinement. Qi and blood are the two basic substances of the body. Both originate from the spleen and stomach and kidney essence, which are closely related in production and operation. In the body of HFpEF patients, due to poor qi and blood, the heart is not nourished enough, and its function gradually weakens, leading to heart failure [8]. The heart is closely related to the liver, spleen, lungs, kidney and other organs. In HFpEF patients, due to visceral dysfunction, liver loss and excretion, spleen dysfunction, lung loss, kidney loss of gasification, etc., resulting in insufficient qi and blood production and poor operation, thus affecting the function of the heart. In addition, visceral dysfunction may also lead to water metabolism disorders, forming an internal stopping of drinking water, and further aggravating the symptoms of heart failure. In HFpEF patients, due to imbalance between yin and yang, such as heart yang failure, heart yin deficiency, etc.,

heart dysfunction cannot maintain normal blood circulation and metabolic activities.

### 2.3 TCM Syndrome Analysis of HFpEF

At present, the traditional Chinese medicine syndromes of HFpEF are judged according to experience. Chen Chan et al. [9] studied the TCM syndrome characteristics of HFpEF and found that patients with HFpEF were in the early and middle stages of heart failure, which were closely related to heart, qi and blood stasis. Symptoms such as heart qi deficiency, qi deficiency and blood stasis were common. Zhao Zhiqiang et al. [10] believe that HFpEF syndrome elements of traditional Chinese medicine are based on false standard, false evidence includes qi deficiency, yin deficiency, yang deficiency. Empirical evidence includes blood stasis, phlegm turbidity, water drinking, and the distribution of different symptom factors is also different. In the southern region, qi deficiency, yin deficiency and water drinking are more common, while in the northern region, qi stagnation, wet evil, and fire (hot) evil are more common. HFpEF patients at different stages and regions show different TCM syndromes. Therefore, clinical syndrome differentiation needs to be adapted to people and local conditions. In addition, combined disease and cardiac ultrasound can further judge the TCM syndrome type of HFpEF. When patients with HFpEF are accompanied by cardiovascular diseases such as hypertension and coronary atherosclerotic heart disease, they are mostly qi deficiency and blood stasis. When patients with HFpEF are combined with metabolic diseases such as diabetes and metabolic syndrome, they are mostly qi-yin deficiency [11]. Therefore, through the in-depth analysis of the combined disease, the possible TCM syndrome type of the patient can be preliminarily judged. In patients with qi deficiency and blood stasis from the perspective of cardiac ultrasound, cardiac ultrasound may show characteristics such as reduced left ventricular diastolic function and abnormal ventricular wall movement. Patients with deficiency qi and yin may show ultrasound manifestations such as increased left atrium volume and reduced left ventricular compliance [12].

## 3. Traditional Chinese Medicine Treatment of HFpEF

The treatment of HFpEF in traditional Chinese medicine is guided by the overall concept, emphasizing the principles of “treating the disease” and “reconciling yin and yang”. It not only pays attention to the recovery of patients’ heart function, but also pays attention to the adjustment of the patient’s overall health status. The main pathogenesis of HFpEF is the deficiency. The treatment should focus on nourishing qi and activating blood, nourishing qi and nourishing yin, warming yang and water, comprehensively analyzing the patient’s physique, condition, age, gender and other factors, and formulating a personalized treatment plan.

### 3.1 Nourishing Qi and Activating Blood

Heart main bloodline and heart qi are important factors to ensure the normal operation of heart and blood. Heart qi deficiency cannot transport blood normally, which is the basis of the disease of HFpEF. Heart qi deficiency causes blood stasis due to weak blood transportation. Over time, it causes

blood stasis and water stops internally and becomes edema. Chen Jingjing [13] Through literature analysis, it is found that traditional Chinese medicine *Salvia miltiorrhiza*, *astragalus* and other drugs to nourish qi, blood circulation and blood stasis treatment for HFpEF have a high frequency. Nourishing qi and blood circulation are the main methods to treat this disease. Studies have shown that the representative prescription for invigorating qi and blood circulation, *Buyanghuanwu* decoction, plays a role in improving heart failure by mediating cell apoptosis signaling pathways such as interleukin-6, cysteine aspartate protease 3, and mitogen-activated protein kinase 8, and delays ventricular reconstruction and protects myocardial cells by inhibiting  $\alpha$ -myosin heavy chain transformation [14]. Ma Ailing et al. [15] used the traditional Chinese medicine compound prescription *Shuxin Huoxue* Prescription to treat Qi deficiency and blood stasis HFpEF, which is mainly nourishing qi and nourishing the heart, supplemented by the method of activating blood circulation, removing blood stasis and dissolving turbidity. The results show that *Shuxin* and blood circulation prescription can significantly reduce the patient’s TCM syndrome points and brain sodium peptides, and prolong the walking distance by 6 minutes. Zhang Yuan [16] Use *Qiangxin Tongmai* Prescription to treat patients with HFpEF with depression, which can significantly increase the maximum speed in the early stage of mitral valve diastolic/the maximum speed of atrial systolic period, improve the quality of life of patients and relieve depression. “*Jin Gui Yao Lve*” states: “If the blood is not good, it is water.” In the clinical treatment of HFpEF, *Yiqi Huoxue* prescriptions are often matched with *Lishui* products. According to the vein theory, Wu Yiling proposed the prevention and treatment of HFpEF of “the same treatment and dissipation of qi and blood” and developed *Qiqi Qiangxin* capsules [17]. Peng Lang et al. [18] used the in-hospital preparation to nourish Qi, promote blood and benefit water prescription combined with snail lactone to treat HFpEF in the elderly. The results showed that this prescription is more effective in reducing the patient’s TCM syndrome points and extending 6MWD. Snail lactone is more advantageous to reduce the patient’s N-terminal B-type natripeptide precursor. The combination of the two can effectively treat HFpEF.

### 3.2 Invigorate Qi and Nourish Yin

HFpEF patients have been sick for a long time, their blood circulation is weak, the blood stasis stops, and they can’t make hematopoietic. They consume yin and blood for a long time, resulting in qi and yin deficiency [19]. Relevant studies have shown that *Shenmai* injection, which has the function of benefiting qi and nourishing yin, plays a role in treating heart failure by inhibiting the ventricular reconstruction caused by the renin-angiotensin-aldosterone system, mediating the uptake and utilization of metabolic substrates, and improving the energy metabolism disorders of patients [20]. The clinical results of Zhu Huiling [21] show that the treatment of HFpEF by *Xinyin* prescription cut from *Shengmai* divergence can further prolong patients by 6MWD and reduce NYHA cardiac function classification. *Yixinshu* capsule is made from the addition, subtraction and subtraction of *Shengmai* powder. Yuan Simin [22] Using *Shengmai Sanhe Guizhi Licorice Longmu* Decoction to treat HFpEF in the elderly, which can reduce the patient’s NT-proBNP, prolong 6MWD, and

improve cardiac function and traditional Chinese medicine symptoms by nourishing qi and yin. Long-term poor control of blood pressure leads to abnormal heart structure and function. The 2021 ESC guidelines emphasize the importance of diagnosis and treatment of HFpEF risk factors such as hypertension and coexisting diseases [23]. Traditional Chinese medicine believes that the disease of hypertension is mostly deficiency, qi and yin deficiency, liver and kidney yin deficiency, etc. are important pathons. Long-term patients also have heart yin consumption, which is similar to the qi and yin deficiency HFpEF. Studies have shown that Shengmaisan drugs can protect myocardial tissue, improve heart microcirculation and regulate blood pressure in both directions [24]. Some studies have discussed the pathogenesis of HFpEF in combination with modern medicine, and believe that heart qi deficiency and evil myocardial are the pathogenesis. Therefore, the method of benefiting qi and nourishing yin, detoxifying and dissipating blood stasis is proposed. The self-developed astragalus heart-protecting soup can significantly reduce the patient's brain sodium peptide, prolong 6MWD, and improve cardiac function [25].

### 3.3 Wenyang Lishui

HFpEF patients have pathological products such as heart qi deficiency, endogenous water drinking and blood stasis. Heart qi deficiency damages the heart yang for a long time, yang deficiency cannot be transformed into water, and if the water is not warm, the water will be retained. The method of warming yang is often used to benefit the water. Research shows that 8 key active ingredients, such as ginseng saponin RH2, rhintonin and xin in compound Zhenwu granules (Zhenwu decoction plus salvia ginseng and red ginseng) improve heart failure through mechanisms such as collaborative anti-inflammatory, inhibiting ventricular reconstruction and regulating the energy metabolism of the myocardium [26]. Wu Xin [27] observed the clinical effect of Qiangxin capsule in the treatment of senile Yang deficiency water generic HFpEF. The results showed that the patient's asthma, edema and other symptoms improved significantly, and the level of plasma brain sodium peptide decreased. Na Ri and other [28] studies showed that compared with standard treatment, the clinical treatment of positive deficiency HFpEF was based on positive and positive drugs. The results showed that 6MWD and quality of life scores were significantly improved. Blood stasis runs through the course of HFpEF. In clinical practice, Wenyang Lishui and the method of promoting blood circulation and removing blood stasis can reduce the pathological product of blood stasis and block the pathological link of blood stasis. Tan Julang [29] uses warm heart prescription to treat HFpEF. The prescription is made of Zhenwu decoction, Baoyuan decoction and Taohong Siwu decoction, so as to warm the yang, promote blood circulation and benefit water, which can reduce the patient's NT-proBNP, soluble growth stimulation expression gene 2 protein and other indicators, significantly improve the patient's quality of life and improve exercise tolerance. Although the symptoms of Yang deficiency water are more cold, excessive use of warm yang products may stimulate the sympathetic nerve and increase the heart load. Therefore, clinical syndrome differentiation with yin nourishing drugs may improve the patient's prognosis from a long-term perspective [18].

### 3.4 Other Treatment Methods

(1) Acupoint application treatment: As one of the important means of auxiliary treatment of traditional Chinese medicine, acupoint application is mainly based on the principle of invigorating qi, promoting blood circulation, removing phlegm and promoting dampness. The commonly used acupoints include Xinyu, Fuzhong, Neiguan and Zusanli, etc. Xinyu acupoint is located on the back, close to the heart, which has the effect of calming the mind and regulating qi and blood. The middle acupoint is located in the chest, which can widen the chest, relieve phlegm and disperse knots. Neiguan acupoint is located in the forearm, which has the effect of calming the mind and reconciling qi and blood. Zusanli acupoint is located in the calf, which can strengthen the spleen, nourish qi, nourish deficiency and strength. By applying special drugs to specific acupoints of the body, with the help of the penetration effect of drugs and the stimulating effect of acupoints, dredge meridians and regulate the function of the viscera to achieve the purpose of treating diseases. It has the advantages of simple operation, few adverse reactions and high safety [30]. Acupoint application is based on the meridian system of the body. According to the specific condition and physique of the patient, the relevant acupoints are selected and appropriate traditional Chinese medicine formulas are selected for application.

(2) Traditional Chinese medicine characteristic exercise therapy: As an important part of traditional Chinese medicine, traditional Chinese medicine characteristic exercise therapy is not only a way of exercise, but also a unique therapy that combines traditional Chinese medicine theory and exercise practice to effectively regulate the balance of qi and blood, yin and yang. Traditional Chinese medicine believes that the health of the body is closely related to the circulation of qi and blood, the function of viscera, and the smoothness of meridians. Traditional Chinese medicine's characteristic exercise therapy regulates the balance between yin and yang of the body through specific movements and breathing methods, promotes the circulation of qi and blood, dredges meridians, and enhances the function of the viscera [21]. Li Xinyue et al. [32] divided 100 HFpEF patients who met the selection criteria into two groups according to the random number table method. The patients in the control group were given conventional drugs to cooperate with health education. The patients in the observation group cooperated with Baduanjin on the basis of the control group and intervened for a total of 3 months. The results showed that combined with Baduanjin can improve the symptoms of dyspnea, edema, fatigue, palpitations, loss of appetite, dizziness, chest tightness and increased body mass in HFpEF patients, regulate cardiac function and improve the quality of life of patients.

## 4. Summary

Syndrome differentiation and treatment is one of the basic principles of traditional Chinese medicine. At present, HFpEF does not have authoritative syndrome differentiation criteria, which is not conducive to clinical standardized drug use, which in turn affects the observation of curative effect. Therefore, it is indispensable to explore the standardized TCM syndrome differentiation system of this disease through

large-scale case research in the future. Restricted by molding methods, it is difficult for HFpEF animal models to restore the complex pathological mechanisms of the disease, which brings many difficulties to further clarify the action mechanism of complex Chinese medicine compound ingredients, or focus on the basic research of prescription monomer components. HFpEF patients have a variety of dysfunctions and phenotypic heterogeneity, which brings many difficulties to modern medical treatment. Although a large number of clinical studies have found that the addition of traditional Chinese medicine syndrome differentiation on the basis of standard treatment can further alleviate the symptoms of HFpEF patients, improve cardiac function, and inhibit the progress of myocardial reconstruction to a certain extent, most HFpEF traditional Chinese medicine has a small scale, a short observation cycle, and fewer long-term efficacy observation indicators. Among them, traditional Chinese medicine syndromes and cardiac function classification are mostly used as the main clinical efficacy observation indicators, and lack objectivity and quantitative analysis. Therefore, in the future, it is necessary to further strengthen the basic research and clinical trials of HFpEF by traditional Chinese medicine, and improve the understanding and accuracy of its pathological mechanism of traditional Chinese medicine. In addition, it is necessary to carry out large sample size and multi-center research to further observe the long-term effect of traditional Chinese medicine treatment of HFpEF, so as to provide more basis for traditional Chinese medicine treatment.

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