

# Research Progress of Traditional Chinese Medicine in Preventing and Treating Ventricular Remodeling by Intervening RAAS System

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## Abstract

Chronic heart failure is a series of clinical syndromes in which a variety of cardiovascular diseases develop to the end-stage. Renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathological development of chronic heart failure, especially its influence on ventricular remodeling, which is the cause of further occurrence and development of a variety of cardiovascular diseases. With the aggravation of aging in China, the population of ventricular remodeling caused by various cardiovascular diseases has increased rapidly in recent years. The incidence of a series of cardiovascular diseases caused by ventricular remodeling is also greatly increased. RAAS system through the intervention of traditional Chinese medicine, regulate the angiotensinII (Ang II), aldosterone (ALD) and so on to improve ventricular remodeling of chronic heart failure to control the research of the progress of heart failure have certain progress, the author collected in recent years through the intervention of traditional Chinese medicine prevention and treatment of ventricular remodeling RAAS system to prevent a series of research achievements of the occurrence of cardiovascular disease, including compound preparations and single herbs from different phase of the intervention of RAAS system mechanism, and the prevention and treatment of ventricular reconstruction by intervention RAAS system of traditional Chinese medicine and its cause of diseases of the cardiovascular system made a summary and outlook.

## Keywords

Traditional Chinese Medicine, RAAS System, Chronic Heart Failure, Ventricular Remodeling

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Chronic heart failure is caused by various basic diseases such as coronary heart disease, hypertension and other changes in the structure and function of the heart, resulting in reduced ventricular ejection and filling capacity, its clinical manifestations are mainly dyspnea and fluid retention. With the aging of China's population, its morbidity and mortality are also increasing year by year [1]. Ventricular remodeling is an irreversible change in cardiac function caused by changes in cardiomyocytes and cardiomyocyte matrix during the development of various cardiac diseases. Ventricular remodeling is also an important pathological basis for the further development and deterioration of chronic heart failure [2], as well as the pathological basis for other cardiovascular diseases. Ventricular remodeling can be caused by activation of neuroendocrine system, activation of cytokines and abnormal gene expression [3]. With the development of the disease, these causes lead to different degrees of hyperplasia, apoptosis and fibrosis of cardiomyocytes and ultimately lead to ventricular remodeling.

## 1. RAAS system and Chronic heart failure

RAAS system has a regulatory effect on cardiovascular system. In the early stage of heart failure, RAAS system synergies with other compensatory mechanisms to improve cardiac output and increase peripheral vascular contraction to mitigate tissue and organ damage. The RAAS system originates from renin synthesis. Reduced cardiac output reduces renal blood flow and activates the RAAS system. Renin is synthesized and released in paracronal cells and converted into angiotensin i (Ang i) under the action of angiotensin converting enzyme (ACE). Ang i is converted into angiotensin ii (Ang ii) with high activity under the action of angiotensin converting enzyme (ACE) [4]. The increased concentration of Ang ii in plasma and cardiomyocytes leads to vasoconstriction and promotes myocardial hypertrophy and fibrosis [5]. Heart failure early in Ang II, under the action of increased cardiac output and peripheral vascular contraction, at the same time Ang II acting on the adrenal cortex, promote the ALD release, formation water sodium retention, along with inflammation, oxidative stress, a series of reactions such as catecholamine release, increase the effective circulating blood volume, ensure the cardiac output perfusion of important organs and tissues, It plays a role in alleviating the signs and symptoms of heart failure. With the further development of heart failure, the RAAS system is over-activated. Under the action of Ang ii and ALD, the cardiac load is increased, and the damage and apoptosis of myocardial cells are aggravated, resulting in ventricular remodeling, which further worsens the heart function and aggravates the heart failure [6].

## 2. RAAS system and the formation and development of ventricular remodeling

Activation of RAAS system plays an important role in the formation and development of ventricular remodeling, in which Ang ii is the main agent. After the activation of RAAS system, the content of Ang ii increased, and Ang ii could promote myocardial hypertrophy, myocardial interstitial fibrosis and myocardial apoptosis by binding to highly specific receptors on the surface of cell membrane [7]. The receptors that bind to Ang ii mainly include Ang ii type 1 (AT1) and Ang ii 2 (AT2). The activity of AT1 is higher than that of AT2, and AT1 is distributed in adrenal gland, vascular smooth muscle, kidney and heart [8]. The vasoconstriction and osmotic pressure regulation of Ang ii is accomplished through specific binding to AT1 receptor. The process is that Ang ii binds to AT1 receptor, promotes the release of other cytokines through intercellular signal transduction, and causes cardiac myocytes to undergo apoptosis, hypertrophy and fibrosis, thus producing the pathological basis of ventricular remodeling [9]. Ang ii can not only bind to receptors, but also mediate ventricular remodeling. The single mediated effect of Ang ii was mainly reflected in the enhancement of proto-oncogene expression in cardiomyocytes, which resulted in the cytological basis of ventricular remodeling and ultimately resulted in ventricular remodeling [10]. Ang ii can also stimulate the release of other factors, such as endothelin, interleukin and tumor necrosis factor, and participate in the process of ventricular remodeling [11]. Ang ii and ALD play a synergistic role in ventricular remodeling. At the same time, studies have shown that ALD alone plays an important role in the development of ventricular remodeling. The mechanisms of ALD involved in ventricular remodeling mainly include oxidative stress, Na<sup>+</sup>-proton exchange protein, NADPH oxidase, Na<sup>+</sup>-K<sup>+</sup>-ATPase inhibition and Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> transporter activation [12]. ALD can also aggravate ventricular remodeling by increasing collagen in cardiomyocytes. The main mechanism of action is that ALD receptor complex binds with DNA in the nucleus, resulting in increased synthesis of type I and type III collagen in cardiomyocytes and decreased degradation rate of collagen, resulting in myocardial fibrosis and aggravating ventricular remodeling. ALD can also increase the level of brain natriuretic peptide (BNP) and serum type III procollagen aminopeptide (PIIINP), which leads to cardiac hypertrophy and ventricular remodeling [13].

## 3. Traditional Chinese medicine affects ventricular remodeling by intervening RAAS

No records about “heart failure” of disease of traditional Chinese medicine, according to its clinical symptoms can be classified as “palpitation”, “edema”, “gasping syndrome” category, such as drag in heart, lung, spleen, kidney and other organs, the basic pathogenesis is the deficiency of Yin and Yang qi of heart, viscera function disorder, heart displaced, based on Yin and Yang deficiency of qi and blood, phlegm turbidity and blood stasis, mutual knot of drinking water standard. Most of them are caused by congenital deficiency or old age, physical decline, invasion of external evil and other reasons to damage the heart and qi, and the heart and blood dysfunction, phlegm, water drinking stop, injury and spleen and kidney for a long time.

### 3.1 Traditional Chinese medicine Prescriptions

#### 3.1.1 Qiliqiangxin capsule

Qiliqiangxin capsule with beneficial temperature Yang Huoxue li shui effect, clinical for improving the symp-

toms of heart failure patients have obvious effect. Ye Yong et al. evaluated cardiac echocardiography, hemodynamics, plasma and myocardial cell Ang ii concentration in mice by drug treatment of myocardial hypertrophy mouse model. Results show that the stilbene Li capsule of TCA postoperative cardiac hemodynamics in mice had no effect, but can inhibit plasma and the myocardial cell Ang II rise, to the prevention and treatment of left ventricular wall thickening and fibrosis area increases, the new cells can also inhibit the expression of AT1 receptor and intercellular signaling and hypertrophy gene expression, inhibit the occurrence of myocardial hypertrophy. It can be known that qiliqiangxin has inhibition of myocardial hypertrophy, improve ventricular remodeling to treat heart failure, this effect and qiliqiangxin through affecting the expression of Ang ii and AT1 receptor to inhibit the activation of RAAS system [14]. Yang Yang et al. dilated cardiomyopathy clinical trial, the results found that take Qiliqiangxin capsule patients serum Ang ii, MMP-2, MMP-9 levels are lower than other, LVEF is higher than other patients, which can be known qiliqiangxin capsule can inhibit the expression of Ang ii, so as to prevent myocardial fibrosis, prevent ventricular remodeling, Relieve heart failure and improve the signs of heart failure [15]. In recent years, there are studies that qiliqiangxin capsule can delay the process of heart failure by regulating lipid metabolism disorders. Qiliqiangxin capsule can inhibit the activation of RAAS system, diuresis, diastolic blood vessels are related to the regulation of lipid metabolism disorders [16].

### 3.1.2 Astragalus membranaceus decoction

Astragalus membranaceus decoction is composed of safflower, astragalus membranaceus and Dangshen, etc. It has functions of promoting blood circulation and removing silt, invigorating qi and strengthening heart. Lu Lei gave the rat model of dilated cardiomyopathy with Huangqi Baoxin Decoction. The changes of left ventricular structure and function were detected by ultrasonic electrocardiogram, and the levels of serum Ang ii, ALD and Renin activity (Renin) were detected. The results showed that the levels of Ang ii, ALD and Renin in serum of low, medium and high dose huangqi Baoxin decoction group were decreased, and the myocardial cells were arranged in order, and the proliferation of fibrous tissue was reduced. The effect of low, medium and high dose was positively correlated with dose, and the high dose group was the best. It can be concluded that Huangqi Baoxin Decoction can prevent myocardial cell proliferation, inhibit ventricular remodeling, improve cardiac function and prevent myocardial fibrosis and cardiac failure caused by DCM by inhibiting activation of RAAS system. Lu Lei prepared low -, medium -, high - drug - containing serum of Huangqi Baoxin Decoction and Ang ii group. Apoptosis myocardial cell model induced by Ang ii was established. Apoptotic cardiomyocytes induced by Ang ii in drug-containing serum. After 24 hours of culture, the apoptosis level of serum was detected, and the expression level of proteins related to apoptosis was detected. It was found that the apoptosis level of cardiomyocytes induced by Ang ii was higher than that of normal cardiomyocytes, and the expression level of proteins related to apoptosis was also increased. Compared with Ang ii induced cardiomyocyte group, the expression of pro-apoptotic factor-related proteins and anti-apoptotic factor-related proteins were increased in high, medium and low drug serum groups, and apoptosis levels were decreased to varying degrees. It can be concluded that Huangqi Baoxin Decoction can prevent and cure ventricular remodeling, and the mechanism is to inhibit endoplasmic reticulum stress (ERS) pathway by inhibiting Ang ii, and play the role of inhibiting apoptosis pathway [17]. Zhang Q et al. found through experimental study that Huangqi Baoxin Decoction can effectively reduce the contents of NT-PRO BNP, IL-6, TNF- $\alpha$ , MMP-2 and MMP-9 in serum, thereby reducing cardiac fibrohyperplasia, improving cardiac morphology and function, and preventing and controlling ventricular remodeling [18].

### 3.1.3 Prescriptions for invigorating qi and promoting blood circulation

The prescription for invigorating qi and promoting blood circulation is composed of safflower, salvia miltiorrhiza, astragalus membranaceus and other traditional Chinese medicines with beneficial effects of qi and promoting blood circulation. The contents of Ang ii, protein kinase C(PKC) and AT1 receptor mRNA in myocardium were determined four weeks after treatment. The ultrastructural changes of myocardium were also detected. It is concluded that Qiangxintongmai pill can reduce Ang ii and AT1 receptor mRNA expression, inhibit the activation of RAAS system, improve cardiac tissue structure and correct heart failure [19]. Zhu BO proved that Xinshuai i formula granule can improve clinical symptoms and quality of life of patients with heart failure through clinical study on patients with heart failure. At the same time, the rat model of heart failure was established and animal experiments were carried out. The conclusion was that xinshuai formula i could reduce the degree of myocardial fibrosis and improve heart failure in rats, which was related to the inhibition of RAAS system, the decrease of linatide and endothelin, and the improvement of hemodynamics [20]. Zhang Z G found that Yiqi huoxue jiadu can reduce myocardial cell apoptosis and improve ventricular remodeling. This mechanism is by increasing mirNA-21 level and decreasing the expression of target protein PTEN, thus inhibiting the completion of p38MAPK signaling pathway [21].

### 3.1.4 Beneficial temperature Yang recipe

Represented by Zhenwu Decoction, the prescription for supplementing air temperature and Yang has the effect of promoting qi and blood circulation, warming Yang and strengthening the heart, and has a significant clinical effect on edema and asthma syndrome of heart and kidney Yang deficiency. Wang hong for heart failure rat model, for replenishing qi, this medicine group, to fill the stomach, heart of rats was detected in LVEF value, after myocardial tissue renin, Ang II, ALD content, safely draw the conclusion that good temperature Yang drug use can be inhibiting RAAS system, improve heart function, and longer duration of drug effect is more significant, good temperature Yang medicine combination alone after use effect is obvious [22]. Gao Y et al. Rat model of myocardial infarction was established, and jiashen formula (Xiangjiapi, Astragalus membranaceus, salvia miltiorrhiza, Notoginseng, Mother Wort, Cassia twig, etc.) was given. LVESD, LVEDD, PWT, LVEF, BNP, Ang ii contents in myocardial tissue were observed 4 weeks later. It can be concluded that Jiashen Prescription can improve the systolic function of heart and ameliorate heart failure by inhibiting Ang ii and improving ventricular remodeling [23]. Zou YAN established a rat model of heart failure with heart-kidney-yang deficiency. Zhenwu Decoction was administered intragastric, and the EF value, serum MMP-9 and TIMP-1 of the rats were measured, and the expression of Ang ii, ALD and AT1 proteins in myocardium were determined. The results showed that the levels of Ang ii, ALD and AT1 in middle and high dose zhenwu Decoction group and western medicine group were decreased simultaneously, and the effect of high dose Zhenwu Decoction group was more significant than middle dose zhenwu Decoction group and Western medicine group. It can be concluded that Zhenwu Decoction can reverse ventricular remodeling and improve cardiac function, which is related to the inhibition of RAAS system [24].

At present, there are still some TCM prescriptions that have achieved remarkable clinical results in treating heart failure and improving cardiac function of patients, but whether the mechanism of action is related to RAAS needs to be further discovered by clinical and laboratory experiments. Qi Jia Wuling Decoction (Astragalus membranaceus, Radix tetraflorrhizae, Poria cochlear, Alisma alismatifolia, Atractylodes atractylodes, Plantago plantarum, poring, turtle plate, turtle root, xiangjia skin, zhi Glycyrrhiza) is the clinical experience of 30 years summed up by Chief physician Zhi Liqin in the treatment of heart failure, clinical has a role in the improvement of symptoms and indicators of chronic heart failure patients. Clinical application of Qijia Wuling Decoction in patients with chronic heart failure has a certain effect on reversing cardiac enlargement, which is related to the fact that Qijia Wuling Decoction can increase LVEF, decrease LVESD and improve LVEDD in mice with heart failure. Whether Qijia Wuling decoction can reverse ventricular remodeling by affecting RAAS system needs further study. Yiqi Xiefei Decoction can protect myocardium, reduce myocardial fibrosis, prevent ventricular remodeling and prevent the progression of heart failure by reducing the expression level of relevant proteins in myocardium tissue and preventing myocardial apoptosis. Jianzhong Qiangxin granule can reduce ventricular preload and improve ventricular remodeling, whether its process and mechanism are related to inhibition of RAAS system needs further study.

### 3.2 Single taste traditional Chinese medicine (TCM)

In recent years, the research of pharmacology of Traditional Chinese medicine has become more and more hot. Panax notoginseng (Panax notoginseng) has the effect of dispersing stasis, stopping bleeding, reducing swelling and settling pain. It is commonly used in traditional Chinese medicine prescriptions to treat bruises, swelling and pain. Modern studies have found that total saponins of Panax notoginseng, the most important active ingredient in panax notoginseng, can reduce blood pressure, dilate blood vessels, improve myocardial fibrosis and reverse ventricular remodeling. The basic principle is that total saponins of Panax notoginseng can inhibit the expression of type i and type iii collagen by regulating TGF- $\beta$ /Smads pathway, thus improving ventricular remodeling. Chinese medicine ginseng has the effect of tonifying qi, often used in various viscera qi deficiency symptoms, modern pharmacology study found that the main active ingredients in ginseng ginseng total saponins for the improvement of the ventricular remodeling after myocardial infarction (mi) has a certain effect, its mechanism is mainly ginseng total saponins for RASS system has a certain inhibitory effect, also has effect on cardiac hemodynamics, The synergistic effect of the two can inhibit ventricular remodeling. Salidroside, the active ingredient of rhodiola rosea and tanshinone, the active ingredient of Traditional Chinese medicine salvia miltiorrhiza have been found to improve ventricular remodeling.

## 4. Conclusion

In recent years, prevention and treatment of ventricular remodeling has become an important therapeutic method to improve the symptoms and signs of heart failure, prevent the further development of chronic heart failure, and improve the cardiac function. At present, western medicine mainly focuses on improving myocardial energy meta-

bolism, regulating the neuroendocrine system and reducing the degree of myocardial cell fibrosis and necrosis. Drug therapy was mainly used, including angiotensin converting enzyme inhibitors (ACEI),  $\beta$ -blockers, aldosterone receptor antagonists, etc. At the same time, some patients received surgical treatment such as ICD and CRT.

TCM also has good effects on improving cardiac function and preventing and treating heart failure by improving ventricular remodeling. The study on the mechanism of TCM improving ventricular remodeling is the only way to scientifically use TCM, give better play to the role of TCM, and improve prescription medication to strengthen therapeutic effect. Traditional Chinese medicine has made some progress in the mechanism of improving ventricular remodeling by affecting neuroendocrine system, changing cellular information transmission pathway and intervening myocardial energy metabolism. But in improving ventricular remodeling of traditional Chinese medicine to treat heart failure mechanism of research still has certain limitations, as a combination of traditional Chinese medicine targets and mechanisms of its effective monomer, accurate is unclear, dialectical treatment of TCM treatment of heart failure ventricular remodeling study is less, as drug ventricular remodeling of traditional Chinese medicine clinical research is less, and the western medicine combined application study is less, This is a problem to be solved to promote the wide application of TRADITIONAL Chinese medicine in patients with heart failure.

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