

Progress in Traditional Chinese and Western Medicine Research on Heart Failure with Diuretic Resistance

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Abstract: Chronic heart failure (CHF) remains a serious clinical and public health problem today, and is the ultimate destination for all types of heart disease. The prevalence of CHF is high, the disease is severe, the prognosis is poor, and the morbidity and mortality rate is high. Patients with CHF often suffer from fluid retention, and diuretics play a key role in the treatment of CHF, but nearly 38% of patients develop diuretics resistance during the course of treatment. Diuretic resistance is gradually becoming a major problem in cardiovascular disease. Diuretic resistance is gradually becoming a thorny problem in the treatment of cardiovascular diseases, so the effective treatment of diuretic resistance is a topic worthy of in-depth study. This article elaborates on the definition and mechanism of diuretic resistance, and discusses the understanding of Chinese medicine on this disease, in order to provide reference for the clinical treatment of chronic heart failure with diuretic resistance.

Keywords: Chronic heart failure; Diuretic resistance; Research progress

1. Introduction

Chronic heart failure (CHF) is a group of complex clinical syndromes caused by abnormal changes in the structure or function of the heart due to a variety of reasons, which makes the ventricular systolic and/or diastolic dysfunction, thus causing a group of complex clinical syndromes, mainly manifested as different degrees of dyspnoea or malaise, fluid retention (pulmonary stasis, corporal circulation stasis and peripheral oedema), etc., and it is the final destination of a variety of cardiovascular diseases, with a high prevalence and a severe condition, poor prognosis. In the China Cardiovascular Health and Disease Report (2020), it is projected that the number of heart failure patients in China has reached 8.9 million ^[1], and the prevalence of chronic heart failure increases significantly with age, and the in-hospital mortality rate of heart failure patients in China is still as high as 4.1% ^[2].

Diuretics are critical and fundamental to the optimal efficacy of heart failure medications and are essential in the routine management of heart failure. Diuretics should be used in all heart failure patients with evidence of fluid retention (I, C recommendation). The use of diuretics can effectively eliminate water and sodium retention, alleviate the symptoms of patients with heart failure, improve exercise tolerance, and thus improve the quality of life of patients. However, with the widespread use of diuretics, it has been clinically found that about 38% of patients are unable to effectively control fluid retention, i.e., diuretic resistance (DR), despite the use of high doses of diuretics ^[3]. DR occurs most often in the stage of acute decompensated heart failure, and is often accompanied by the exacerbation of clinical heart failure symptoms and signs, such as telangiectasia, markedly worsening oedema, and progressive weight gain. Diuretic resistance has now become a stumbling block in the treatment of heart failure, and is an independent predictor of deterioration, post-discharge mortality, and increased readmission rates for heart failure in patients with heart failure.

2. Western medicine's understanding of chronic heart failure with diuretic resistance

2.1. Definition of diuretic resistance

There is no single accepted definition of diuretic resistance (DR), but it is most often referred to as "failure to reduce congestion despite adequate and increasing doses of diuretics". With regard to chronic

heart failure with DR, the following diagnostic criteria are referred to: urine output $<0.5-1.0$ mL/(kg-h) after daily intravenous furosemide doses ≥ 80 mg or equivalent diuretics; or the following criteria are met: (1) persistence of stasis despite the use of high-dose diuretics (intravenous furosemide ≥ 80 mg/d); (2) urinary sodium/glomerularly filtrated sodium $< 0.2\%$; and (3) urinary sodium excretion < 90 mmol in 72 h despite oral furosemide 320 mg daily.

2.2. Commonly used diuretics

2.2.1. Diuretics with tabs

Collaterals are the backbone of diuretic therapy for heart failure and are used in more than 90% of heart failure patients. They are mainly used by inhibiting the active reabsorption of NaCl in the thick-walled segment of the medullary collaterals of the renal tubule. It is indicated in most patients with heart failure, particularly in those with significant fluid retention or with impaired renal function (eGFR < 30 ml/(min-1.73m²)). Includes furosemide, torasemide, bumetanide. (40mg furosemide, 20mg torasemide, 1mg bumetanide have comparable diuretic effects.) The most commonly used clinically is furosemide, which has a linear dose-effect relationship; torasemide and bumetanide have better diuretic effects in some patients due to their higher oral bioavailability. Intravenous dosage forms are more effective when fluid retention is significant, and should also be given as early as possible, as early administration of collaterals diuretics reduces in-hospital mortality.

2.2.2. Thiazide diuretics

Mainly by inhibiting the reabsorption of NaCl in the anterior segment of the distal tubule and the proximal tubule. Weaker than the label diuretics, it is only indicated in heart failure patients with mild fluid retention, with hypertension and normal renal function. Thiazide diuretics are diminished in patients with reduced renal function [eGFR < 30 ml/(min-1.73m²)] and are not recommended. However, in patients with intractable oedema (furosemide dosage greater than 80 mg per day), thiazide diuretics may be used in conjunction with label diuretics. This includes hydrochlorothiazide and indapamide.

2.2.3. Aldosterone receptor antagonists

Acts mainly on distal tubules and collecting ducts, blocking Na⁺-K⁺ and Na⁺-H⁺ exchange and reducing Na⁺, Cl⁻ and water reabsorption. The diuretic effect is weak, and diuretic resistance can be improved by combining with a label diuretic. Such as spironolactone.

2.2.4. Vasopressin V2 receptor antagonists

It mainly antagonises the action of antidiuretic hormones, improves free water clearance and urinary excretion, reduces the osmolality of urine and ultimately contributes to an increase in serum sodium levels. Recommended for patients with poor results of conventional diuretic therapy, hyponatraemia or a tendency to renal impairment. The representative drug is tolvaptan.

2.3. Mechanistic studies of DR in heart failure combined with DR in Western medicine

2.3.1. Changes in diuretic potency and pharmacokinetics

There is a clear quantitative effect curve for the onset of diuretic effect of tabs [4], i.e., the diuretic effect intensifies as the diuretic dose increases. In patients with CHF, the diuretic threshold dose increases and the time to peak and half-life are prolonged, whereas diuretics must be at a certain threshold concentration to be effective, thus making it more difficult to achieve the previous effect with the same dose and ultimately producing diuretic resistance.

2.3.2. Diminished diuretic absorption

Chronic heart failure is associated with significant body circulation stasis in all end stages of disease progression, leading to digestive tract stasis and cellular oedema, in which case the absorption of oral diuretics in the gut is reduced, and their diuretic effect decreases, making it take longer for the drug to reach its effective threshold, and consequently diuretic resistance occurs.

2.3.3. Sodium retention after diuresis

Diuretics require a relatively stable drug concentration to be effective, and when the effective tubular concentration of some diuretics with a short half-life is below the diuretic threshold, compensatory Na⁺ reabsorption will occur in all segments of the renal tubule, a phenomenon known as post-diuretic sodium retention [5], and at the same time, when the concentration of diuretics is lower than that of the effective

concentration, the diuretic effect will be counteracted by the effect of post-diuretic sodium retention, which will in turn increase the chances of diuretic resistance occurring.

2.3.4. Hyperplasia and hypertrophy of distal tubular epithelial cells

Prolonged use of collaterals diuretics inhibits sodium reabsorption, leading to the transport of large amounts of Na⁺ to the distal tubule, stimulating the microstructure of the distal tubule and collecting duct epithelial cells, causing compensatory hypertrophy, and ultimately enhancing water and Na⁺ reabsorption, leading to increased water and sodium retention and a diminished effect of diuretics.

2.3.5. Increased renal tubular resistance

Ter Maaten et al [6] showed that increased renal tubular resistance is more of a major cause of collaterals diuretic resistance compared to decreased diuretic transit.

2.3.6. Cardiorenal syndrome

Late decompensation in heart failure leads to impairment of renal function, which then further aggravates heart failure in a vicious circle, this is the cardiorenal syndrome. Chronic heart failure undergoes hyperactivation of the RAAS system and the neuroendocrine system, reduced renal blood flow, and inflammatory factor effects, which ultimately lead to impairment of glomerular filtration, tubular function, and neuroendocrine function, which leads to diuretic resistance.

2.3.7. Drug interactions

Non-steroidal anti-inflammatory drugs can reduce the synthesis of prostaglandins by inhibiting the enzyme cyclooxygenase. (Commonly used collaterals diuretics, such as furosemide, are used to reduce the activity of prostaglandinolytic enzymes, thereby increasing the amount of prostaglandins in the body, and thus exerting a diuretic effect.) , which in turn affects the diuretic effect; penicillin, antihistamines, methotrexate, etc. reduce the diuretic effect due to the similarity of the transport pathway with the label diuretics; some experiments have proved that the diuretic effect of furosemide decreases when it is used together with probenecid [7].

2.3.8. Hyponatremia, hypochlorhydria, hypoproteinaemia

High levels of aldosterone in the body produce significant water and sodium retention, increasing the risk of diuretic resistance, of which hyponatraemia is one of the influencing factors. TerMaaten et al found that hypochlorhaemia affects the therapeutic outcome of patients with CHF, and that the lower the level of chlorine in the blood, the worse the diuretic effect is. Patients with CHF suffer from impaired absorption and synthesis of proteins due to stagnation of the gastrointestinal tract, oedema, etc. And tabular diuretics need to bind to albumin in the body in order to be effective, therefore, hypoproteinaemia can also lead to diuretic resistance.

2.4. Western treatment of heart failure combined with DR

2.4.1. Diuretic administration

(1) Increase diuretic dose or change type

Wang Yong [8] and others used to treat patients with CHF with DR by increasing the dose of diuretics, and the patients' symptoms and signs improved significantly compared with before. However, several studies have shown that high-dose diuretics are more likely to cause electrolyte disorders and abnormal renal function, and there is also evidence-based medical evidence that high-dose diuretics have a poor long-term prognosis for patients with heart failure, so the use of a single high-dose diuretic is not recommended. Patients may choose to change the type of diuretic, such as torasemide, tolvaptan, etc., if they have poor efficacy in long-term use of a tabular diuretic.

(2) Combination of multiple diuretics

The long-term use of tabular diuretics can lead to post-diuretic sodium retention and distal tubular alterations, therefore, combining different kinds of diuretics, e.g., thiazide diuretics acting proximal to distal tubules, is beneficial to improve diuretic resistance due to abnormalities of renal tubular function in a particular segment . Analysis of related literature [9] found that combining different kinds of diuretics to treat diuretic resistance is better than using one diuretic alone, which can reduce water and sodium retention, improve the safety of clinical medication, and reduce the readmission rate.

(3) Changing diuretic dosage forms

Intravenous use of diuretics increases bioavailability and allows complete absorption compared to oral diuretics. Continuous pumping of diuretics facilitates maintenance of drug concentrations and more effectively corrects diuretic resistance. Continuous intravesical administration of collateral diuretics is an effective method of correcting diuretic resistance. Continuous pumping of high-dose diuretics can effectively improve clinical symptoms and cardiac function in patients with heart failure with diuretic resistance [8]. A Meta analysis of diuretic administration by Kuriyama et al suggested that there were no significant differences between continuous pumping of diuretics and intermittent infusion in terms of adverse effects (hypokalemia, hyponatraemia, SCr elevation, and hypotension) and the number of days of hospitalisation and all-cause mortality. There were no significant differences in adverse effects (hypokalaemia, hyponatraemia and hypotension) and hospital days, all-cause mortality.

2.4.2. Combination with other drugs

(1) Drugs to improve renal blood flow

Small doses of dopamine can selectively act on renal arteries, combine with dopamine receptors on renal blood vessels and cause renal vasodilatation, increase renal blood flow, and improve eGFR. Yang Mei et al [10] found that intravenous pumping of small doses of dopamine in combination with furosemide can increase the diuretic effect. Wang Lin et al [11] found that recombinant human brain natriuretic peptide used for diuretic resistance treatment in heart failure can antagonise the RAAS system, which can rapidly improve the patient's symptoms, reduce the water-sodium retention and improve the diuretic resistance. In addition, the combination of prostaglandin and tab diuretics has been shown to have better efficacy in chronic heart failure with diuretics, without significant adverse effects, and can improve the prognosis of patients with chronic heart failure [12].

(2) Serum albumin

In refractory heart failure with hypoproteinaemia, furosemide in combination with human albumin increases plasma colloid osmolality, reduces tissue oedema, and improves diuretic resistance, but it has also been demonstrated that there is no significant correlation between the correction of hypoproteinaemia and improvement in diuresis [13].

(3) Hypertonic salts

Studies have confirmed that hypertonic saline can improve renal function by increasing crystalloid osmolality, increasing circulating blood volume and renal blood flow through hypertonicity, and that the combination of diuretics and hypertonic saline can more effectively improve fluid retention, increase the effect of diuretics, and shorten the length of hospital stay [14].

(4) Glucocorticoids

Combined application of furosemide and prednisone can rapidly eliminate sodium retention, improve clinical symptoms and renal function [15]. However, some scholars are still against the use of glucocorticoids, so further clinical safety and efficacy studies are needed.

(5) Adenosine receptor antagonists

Adenosine acts on the adenosine A1 receptor on the small renal entry arteries to reduce renal blood flow, decrease eGFR and increase water and sodium reabsorption, and adenosine receptor antagonists may improve diuretic resistance by antagonising this process, but it has also been demonstrated that their treatment groups did not show a difference from the placebo group [16].

2.4.3. Ultrafiltration

Extracorporeal ultrafiltration therapy provides precise control of fluid excretion, improves diuretic resistance, shortens hospital stay, reduces decompensated heart failure episodes and heart failure rehospitalisation rates, and is safe and well tolerated. Ultrafiltration has a long history as a complementary treatment to diuretics, but currently ultrafiltration therapy is only used in patients who do not respond to pharmacological treatment.

2.4.4. Other therapies

Including end-stage heart transplantation, haemodialysis filtration, etc. These methods are suitable for those who have persistent symptoms of heart failure or even aggravation of heart failure after active drug treatment; they can be recommended for those who have secondary heart failure or aggravation of heart failure with severe renal insufficiency.

3. Traditional Chinese Medicine's Understanding of Chronic Heart Failure with Diuretic Resistance

3.1. Disease name, etiology, and pathogenesis

3.1.1. Name of the disease

There was no name of "heart failure" in traditional Chinese medicine at first. The "Inner Canon of Huangdi" first described the symptoms of heart failure as "heart distension, dyspnea, shortness of breath, restlessness in bed". Another example is "Su Wen·Bi Lun": "Heart vessel blockage stasis leads to blockage of the heart meridian, restlessness and discomfort in the epigastric region, accompanied by asthma, dry throat, and hiccups. The upward flow of qi can cause fear and unease". "Su Wen·Nidiao Lun" said: "If the heart qi is weak, it can be seen that the panting continues continuously". There is no concept of DR in Chinese medicine, for heart failure combined with DR, according to the clinical manifestations, Chinese medicine will be attributed to "heart water", "palpitations", "gasping evidence", "phlegm-drinking", "oedema" and so on. The descriptions in the "Ling Shu" and "Heartburn, shortness of breath, shortness of breath, and inability to lie down" are more or less the same.

3.1.2. Causes

In the "Inner Canon of Huangdi" has been clarified that its occurrence is mainly related to the deficiency of the body, dietary disorders, external evil attack, emotional disorders, too much thought, excessive fatigue and other factors. For example, the "Su Wen·Qi Tong Tian Lun" said: "If the food consumed is too salty, it can cause damage to bones and muscles, suppress heart qi; If the food consumed is too sweet, it can cause chest distress and short breath". "Suwen·Five viscera generation" said: "Due to the invasion of external evil and excessive contemplation, the heart qi can be damaged. External evil takes advantage of the opportunity to invade the heart and cause heart obstruction"; "Su Wen·Jutong Lun" said: "Overwork can lead to wheezing and sweating, causing both internal and external qi to leak out of the body, resulting in qi depletion". According to the book "Theory of various diseases and origins", "The occurrence of kidney disease is due to both kidney and spleen deficiency", it indicates that the occurrence of heart failure with diuretic resistance is related to organ damage such as heart, kidney, and spleen.

3.1.3. Disease Mechanisms

The "Su Wen" said "If the heart is deficient in qi, it can be seen that the panting continues continuously". And the "Shengji Zonglu" stated that "Overexertion and palpitations are caused by insufficient heart qi, which is called "Water attacking the heart" in TCM. These indicate that heart qi deficiency is the fundamental pathogenesis of heart failure. Deficiency of heart qi can lead to blood stasis due to the weakness of blood circulation; deficiency of heart qi can also lead to qi not transforming water, and water-drinking stops within the heart; and fluid and blood have the same origin, and if the blood is unfavourable, then it will become water, which can lead to the generation of water-drinking. Wang Jing et al. [17] believed that "qi deficiency, blood stasis, and water retention are the basis, the target, and the elephant of heart failure combined with DR", and considered that the formation of heart failure combined with DR is a process in which qi deficiency, blood stasis, and water retention are "complementary to each other and mutually fulfilling". Academician Chen Keji [18] believed that heart failure is caused by the deficiency of heart qi and yang, and the accumulation of pathological products such as blood stasis, phlegm and water, which are summarised as deficiency, blood stasis and water, which are considered to be mutually influencing and causative.

3.2. Traditional Chinese Medicine (TCM)

3.2.1. Traditional Chinese Medicine Compounding

According to Yang Haiyan et al [19], "warming yang and promoting water retention, benefiting qi and activating blood circulation" is the main therapeutic principle for heart failure combined with DR. According to Yu Jiang et al [20], heart qi and heart yang insufficiency caused oedema in heart failure, and the treatment of diuretic resistance with Zhenwu Tang plus flavour could significantly increase the patient's 24 h urine volume and alleviate diuretic resistance. According to Gao Rui et al [21], heart failure combined with DR due to insufficiency of heart yang, deficiency of kidney yuan, and blood stasis and water stagnation, the use of Ling Gui Zhu Gan Tang with added flavour to replenish the deficiency and eliminate blood stasis, promote diuresis and activate blood circulation can significantly increase the 24 h urine output of the patients, improve the cardiac function, and alleviate the symptoms such as oedema.

Shen Ao ^[22] et al. concluded that Zhenwu Tang combined with Ling Gui Jiu Gan Tang plus subtractions adjuvant treatment of chronic heart failure with diuretic resistance had better efficacy, which could improve heart failure and cardiac function without obvious adverse effects. Sun Jingyi ^[23] treated 66 patients with diuretic resistance in HF with yang deficiency and water flooding, the treatment group used Ling Gui Zhen Wu Tang to warm yang and transform qi, diuretics and eliminate oedema, and the control group was treated with conventional western medicine, and it was found that the treatment group was able to effectively improve the symptoms and increase the 24h urine output. Lin Bing et al ^[24] used the method of transforming qi, activating blood and inducing diuresis to improve the neuroendocrine level of patients with acute heart failure and diuretic resistance by using the formula of Baoyuan Tang combined with Haifu yuyu Tang, which improved the diuretic response, improved the symptoms and enhanced the clinical effect. Zheng Yong ^[25] treated patients with heart failure combined with DR with Zhenwu and Ephedra Tang, which warms the yang and induces diuresis, and the decrease of NT-proBNP and the increase of 24h urine output were significantly higher than that of the control group. Yang Xueqing et al ^[26] considered that the pathogenesis of this disease is mainly "internal movement of wind in the complex", and proposed the treatment of "benefiting qi and warming yang, activating blood and promoting diuresis, dispelling wind and clearing the complex", and chose the team's self-designed formula, "No. 2 formula of Luofengning" (Xu Changqing 15) to treat patients with heart failure combined with DR. "Xu Changqing 15 g, Fenghui 15 g, Deer's Tortoise 9 g, Codonopsis Pilosulae 30 g, Radix Astragali 30 g, Radix et Rhizoma Polygoni Multiflori 12 g, Cinnamomum Cassiae 15 g, Salviae Miltiorrhizae 30 g, Poria cocos 30 g, Ze Xie 12 g, Atractylodis Macrocephala 12 g, Magnolia Officinalis 6 g, Pericarpium Citri Reticulatae 15 g, Sandalwood 9 g, Drabanemerosa hebecarpa 9 g, Almonds 10 g, Semenatricium Chrysanthemi 12 g) was chosen to treat patients with diuretics resistant to HF. patients, which was able to increase the patient's urine output, reduce water-sodium retention, and improve diuretic resistance, thereby improving cardiac function. Chen Chen et al ^[27] used Poria, almond, and liquorice soup with added flavour in the treatment of qi deficiency, blood stasis, and water obstruction type heart failure with diuretic resistance, which could effectively reduce the average daily dose of tachyphylaxis, improve their cardiac function, and promote patients' urination.

3.2.2. Proprietary Chinese medicines and Chinese medicinal preparations

Tong Miao et al ^[28] used cardioplegia injection combined with astragalus red capsule to treat heart failure combined with DR, and the patients' Chinese medicine symptom scores improved significantly, urine output increased, and cardiac function improved. Clinical studies have shown that Astragali Drabanemerosa hebecarpa strong heart capsule can increase the patient's urine output and significantly improve cardiac function ^[29]. Li Deqing et al ^[30] through clinical observation of 58 patients with heart failure with diuretic resistance, the results showed that ginseng injection combined with tachycardia can significantly improve heart failure symptoms and diuretic resistance. Xiao Honggang ^[31] and others used Astragalus injection applied to patients with CHF with DR, and the therapeutic effect was remarkable. An experimental study showed that astragalus hebecarpa strong heart capsule treatment of CHF rats after the 1st and 4th weeks of their urine volume increased significantly ^[32].

3.2.3. Traditional Chinese Medicine External Treatment

Heat-sensitive moxibustion ^[33] can improve clinical symptoms, clinical efficacy, urine output and exercise tolerance in patients with heart failure and diuretic resistance. The results of the study showed ^[34] that the combination of acupoint therapy on the basis of conventional western medicine could reduce clinical symptoms, improve cardiac function and LVEF, and significantly reduce NT-proBNP levels in patients with heart failure with dilated cardiomyopathy. Ding Yongyong ^[35] and others used spaced ginger moxibustion to treat patients with diuretic-resistant heart failure with Yang deficiency and water flooding, and the clinical efficacy was remarkable. Chang Liping et al ^[36] made a decoction concentrate of Chinese herbs onion white and pepper, and applied ultrasonic conductivity instrument to introduce into the Shenque acupoint for the treatment of qi (yang) deficiency, blood stasis, and water-flooding heart failure diuretics resistance patients, which can significantly improve the clinical symptoms of the patients, increase the volume of urine, and reduce the application of diuretics and cardiac medications dose.

4. Conclusion

In conclusion, diuretic resistance is a common phenomenon in the clinical treatment of heart failure patients. Through the study of Chinese and Western medicine on diuretic resistance, it is found that Western medicine is constantly expanding new ideas for the treatment of heart failure with diuretic resistance, and Chinese medicine has also embodied its unique therapeutic ideas through the holistic

concepts and system of diagnosis and treatment, and the combination of some external treatments of Chinese medicine has been proved to be beneficial for the treatment of heart failure with diuretic resistance, which can effectively improve the quality of life of patients and improve the long-term prognosis. It can effectively improve the quality of life and long-term prognosis of patients. However, the treatment of diuretic resistance still has a great research prospect, which needs to be further explored.

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