

Research Progress on the Relationship between Heart Failure and Intestinal Microflora in Traditional Chinese and Western Medicine

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Abstract: Heart failure is a group of clinical syndromes caused by dysfunction of ventricular congestion and/or ejection caused by damage to the heart structure or function caused by multiple factors. According to statistics, the number of cardiovascular disease patients in China is about 330 million, of which about 8.9 million are heart failure patients. 83% of patients with heart failure were hospitalized at least once a year, and 43% of patients with heart failure were hospitalized at least 4 times a year. Although anti-heart failure drug therapy based on guidelines can improve the hemodynamics of patients, its tolerance, associated adverse effects, and poor prognosis compel continuous exploration of new therapeutic targets and approaches. It has been found that there is a close correlation between intestinal flora and heart failure. Combined with the relevant knowledge of intestinal flora, many experts put forward the theories of "treating psychological spleen", "intestinal mandrel" and "heart-spleen-intestine theory" to explore the relationship between heart failure and intestinal microflora from the theory of traditional Chinese medicine. It provides more ideas for the diagnosis and treatment of heart failure.

Heart failure is not only the worsening stage and final destination of various cardiovascular diseases, but also the leading cause of death. In recent years, with the progress of China's aging population, the incidence of heart failure has increased, but the rehospitalization rate and mortality rate have not been significantly improved. Research shows that the prevalence rate of heart failure in Chinese adults is about 0.9% ^[1]. The 2018 China Cardiovascular Disease report^[2] clearly pointed out that at present, among the total causes of death of urban and rural residents, cardiovascular disease is the leading cause of death. At the same time, in cardiovascular diseases, the incidence of heart failure continues to increase, and heart failure has become one of the most important cardiovascular diseases. The main pathogenesis of heart failure include sympathetic-renin-angiotensin-aldosterone system mechanism, immune inflammatory response, myocardial remodeling, neuroendocrine mechanism and so on. These mechanisms affect the pathogenesis and prognosis of heart failure. With the in-depth study of the mechanism of heart failure, it is found that

intestinal flora is closely related to the occurrence and course of heart failure. More and more scholars support the effect of intestinal flora on the pathogenesis of heart failure, thus putting forward the hypothesis of intestinal flora in heart failure. In the theory of traditional Chinese medicine, the related theories of heart, spleen and intestine are put forward, such as "heart and small intestine exterior interior", "heart produces blood, blood produces spleen", and "heart receives qi from spleen and spreads to lung". Combined with the relevant knowledge of modern intestinal flora, experts put forward the theories of "treating psychological spleen", "intestinal mandrel" and "heart-spleen-intestine theory" to explore the correlation between heart failure and intestinal flora. Combining modern knowledge of intestinal flora, experts put forward theories such as "treating psychological spleen", "intestinal axis" and "heart-spleen-intestinal theory" to explore the research on the correlation between heart failure and intestinal flora, and theoretically supplement the feasibility and necessity of heart-spleen-intestinal theory in the treatment of heart failure, providing more basis and treatment ideas for the clinical application of heart failure.

1. Study on the relationship between heart failure and intestinal flora

1.1 Common gastrointestinal symptoms in patients with heart failure.

Patients with heart failure often have symptoms such as abdominal distension, abdominal pain, lack of appetite, nausea and vomiting, which greatly affect the quality of life of patients. Heart failure will reduce cardiac output, resulting in reduced intestinal blood flow, resulting in liver stasis or intestinal wall edema and other pathological changes, and finally appear the above gastrointestinal *symptoms*. Related studies have shown that in addition to the above symptoms, constipation and loss of appetite are also common in patients with heart failure^[3]. Some patients even have dyspnea and regurgitation^[4].

1.2 Pathological changes of gastrointestinal tract in patients with heart failure

The cardiac output of patients with heart failure will be reduced. In order to meet the needs of the body, it will first ensure the blood supply of the heart, kidneys, brain and other important organs, and at the same time reduce the blood supply to the limbs and gastrointestinal tract. In the gastrointestinal blood supply, the blood supply of gastrointestinal villi and mucosa accounts for most of the gastrointestinal blood supply, so when gastrointestinal ischemia, it will be highly sensitive to it^[5], showing the symptoms of gastrointestinal ischemia and hypoxia earlier. Intestinal ischemia and hypoxia in patients with heart failure lead to the decrease of gastrointestinal peristalsis and absorption function, which will further lead to the increase of gastrointestinal permeability^[6], resulting in abdominal distension and other symptoms. In addition, sympathetic nerves are widely distributed in the gastrointestinal tract, which participate in the visceral circulation. When sympathetic nerve stimulation increases, it will lead to the contraction of blood vessels and the decrease of intestinal perfusion, resulting in gastrointestinal symptoms such as abdominal distension, abdominal pain, nausea, vomiting and so on^[7].

Related studies have shown that heart failure is related to intestinal epithelial dysfunction, mainly related to intestinal perfusion and ischemia reduction^[8]. Intestinal injury can cause intestinal wall edema, further reduce intestinal perfusion, damage intestinal wall integrity, reduce intestinal gastrointestinal barrier function, enhance bacterial permeability, increase circulating endotoxin and potential inflammation in the body, induced heart failure^[9]. At the same time, the ischemia of intestinal villi leads to the decrease of mucus secretion, the damage of mechanical, immune and mucosal barrier function of intestinal mucosa, the decrease of mucosal defense function, the production of cytokines and further inflammatory reaction^[10]. There is a certain correlation between

chronic inflammatory factors and heart failure. Studies have found that inflammatory factors such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and C-reactive protein (CRP) in patients with heart failure will increase, induce inflammatory response in the body, cause microvascular and myocardial dysfunction, and eventually lead to severe heart failure or cardiogenic cachexia^[11].

1.3 Changes of intestinal microbes during heart failure

Heart failure leads to a decrease in intestinal blood flow, which further leads to intestinal villus ischemia^[12], and finally leads to changes in intestinal permeability and morphology. The study found that the abundance of intestinal flora in the feces of patients with heart failure decreased, Brout and Collins relatively decreased, the number of salmonella, Yersinia, Shigella, Candida, campylobacter increased, the more serious the degree of heart failure, the intestinal beneficial bacteria will decrease, and the intestinal pathogenic bacteria will increase more significantly^[13]. The concentration of bacteria in the intestinal tract of patients with heart failure is significantly increased, causing intestinal hypoxia and changes in PH value, at the same time, it is easier to induce the inflammatory response of the body, thus speeding up the process of heart failure^[14].

1.4 Mechanism of the effect of intestinal flora on patients with heart failure

Related studies have shown that choline, betaine and trimethylamine oxide (TMAO) are important metabolites of intestinal flora. Choline is essential in the process of cell membrane phospholipid, neurotransmitter acetylcholine synthesis and methyl metabolism. Intestinal microflora will convert lecithin choline in diet into trimethylamine (TMA). After trimethylamine is absorbed by the human body, trimethylamine is converted into trimethylamine oxide by flavin monooxygenase (FMO) in the liver^[15].

Choline, betaine and TMAO can all predict the joint end point of heart transplantation and all-cause death, but after excluding some influencing factors, it is found that only trimethylamine oxide has statistical significance^[16]. Studies have confirmed that there is a certain correlation between TMAO and atherosclerosis and heart failure^[17]. The level of TMAO in non-heart failure patients is lower than that in heart failure patients^[18]. And regardless of the cause of heart failure, elevated TMAO levels predict a higher incidence of adverse events^[19]. Studies have found that the increase of TMAO level in the body will accelerate the process of organ fibrosis. For the heart, it is mainly manifested as reducing the left ventricular ejection fraction (LVEF), increasing the level of BNP, inducing pulmonary edema, aggravating myocardial fibrosis, and finally leading to the occurrence of heart failure^[20]. However, the composition of intestinal flora determines the level of trimethylamine oxide^[21]. With the aggravation of heart failure, the concentration of TMAO in the body will gradually increase. Reducing the concentration of TMAO is a very effective measure for the treatment of heart failure, which can improve the prognosis of patients with heart failure^[22].

Related studies have found that during heart failure, bacteria and their endotoxins are absorbed into the blood through the intestines, and the levels of inflammatory factors such as TNF- α , C-reactive protein and IL-6 are significantly increased in patients with heart failure^[23]. Endotoxin is an important factor in the production of these inflammatory factors. The level of inflammatory factors in patients with heart failure is closely related to the prognosis of heart failure. The significant increase of inflammatory factors will accelerate the development of heart failure.

The "intestinal microflora hypothesis" holds that the substances secreted by intestinal microorganisms are closely related to the occurrence and course of heart failure. More and more scholars support the effect of intestinal microflora on the pathogenesis of heart failure, thus putting forward the hypothesis of intestinal microflora in heart failure. The so-called hypothesis of intestinal flora in patients with heart failure shows that the decrease of cardiac output and systemic

blood stasis lead to intestinal edema and ischemia, destruction of intestinal mucosa, increase of intestinal microbial translocation, and changes in microbial composition at the same time. The metabolites that lead to their entry into the blood circulation are also changed accordingly, which may cause or aggravate the systemic inflammatory reaction, resulting in malnutrition and cachexia in patients with chronic heart failure.

1.5 Treatment of intestinal flora in patients with heart failure

The pathophysiological mechanism of heart failure experienced the initial "water and sodium retention" model to "abnormal hemodynamics" model, and then experienced the "neuroendocrine abnormal activation" model. The above research results have widely promoted the reform of the treatment of heart failure.

Based on the in-depth exploration of pathogenesis, aldosterone antagonists, angiotensin II receptor antagonists (ARB), angiotensin converting enzyme inhibitors (ACEI) and β -blockers are the most studied and most important drugs in the treatment of CHF. At the same time of drug therapy, non-drug therapy strategies such as cardiac asynchronous therapy and ICD are also important treatment methods. These drug treatments and non-drug treatments reduce the mortality and improve the quality of life of patients to some extent, but the mortality rate of chronic heart failure (CHF) remains high. At present, more and more experts and scholars support the effect of intestinal flora on the pathogenesis of heart failure. Studies have found that intestinal flora is closely related to the occurrence and development of heart failure. The rapid development of intestinal microbiology provides a new direction for revealing the occurrence of disease and the mechanism behind drug action. Studies have shown that the composition of intestinal flora in patients with chronic heart failure changes, and the number of harmful bacteria increases significantly with the progress of the disease^[24]. At present, there is no significant benefit in the treatment of heart failure by inhibiting inflammation. High levels of TMAO have been found to be closely related to disease progression in patients with heart failure and may be an independent risk factor for heart failure^[25]. Lower plasma TMAO levels may reduce mortality and improve prognosis in patients with heart failure^[26]. Therefore, reducing the production of TMAO through some interventions is expected to be a new treatment for heart failure^[27], including dietary intervention, probiotics and probiotics therapy, fecal transplantation, antimicrobial therapy, etc^[28].

2. Understanding of heart failure and intestinal flora in traditional Chinese medicine

According to the traditional theory of traditional Chinese medicine, chronic heart failure belongs to the categories of "asthma syndrome", "palpitation" and "edema" in traditional Chinese medicine^[29]. Its basic pathogenesis is due to yang deficiency and decline and warm dereliction of responsibility, which leads to the internal stagnation of yin-cold pathogen and internal stagnation of water-dampness and blood stasis, forming the syndrome of deficiency and excess. The disease is located in the heart, adjacent to the lungs, kidneys, spleen and Sanjiao.

By summarizing the ancient books and modern literature of traditional Chinese medicine, modern doctors put forward the theories of "heart-spleen-intestine", "treatment of psychological spleen" and "intestinal axis", which provides a new idea for the treatment of heart failure^[30].

In the theory of traditional Chinese medicine, it is proposed that the disease of heart failure lies in the heart, but among the five internal organs, the five elements of the heart and spleen are born with each other, the meridians of the two internal organs are connected, and the yin and yang of qi and blood are related to each other^[31]. In the pathological changes, the spleen and the heart are inseparable, the heart governs the blood, the spleen dominates the blood, and the deficiency of heart qi affects the blood circulation of the heart, and then affects the movement and function of the

spleen. The five elements theory puts forward that the relationship between the heart and the spleen is the relationship between mother and son, and the deficiency of qi and blood of the heart affects the function of the spleen, which will eventually lead to deficiency of the heart and spleen, showing discomfort such as palpitation, shortness of breath, fatigue, addiction, abdominal distension, belching, hiccup and so on^[32]. In the treatment, the heart and spleen should also be treated at the same time, and the loss of health movement of the spleen is the key to the formation of pathological products such as water, phlegm and blood stasis in heart failure, so invigorating the spleen and replenishing qi, heart and spleen is one of the important measures for the treatment of heart failure.

According to the visceral image theory of traditional Chinese medicine, "large intestine belongs to stomach". However, in TCM theory, spleen and large intestine are not independent viscera, but viscera with close relationship in physiology, pathology, meridians and collaterals. Physiologically, the spleen is the official of the granary, the main transport, the source of qi and blood biochemistry, and the essence of water grain into the necessary qi, blood and body fluid for the human body, scattered in various viscera to maintain normal life activities; the small intestine is the official of popularity, the large intestine is the official of transmission, and the small intestine is cooked by the stomach, which exert its function of secreting clear and turbid. The Qing people spread the whole body through the spleen to nourish his internal organs, and the turbid ones spread the intestine into dregs with the help of the spleen. Pathologically, the dysphagia of spleen leads to the dysfunction of small intestinal secretion of clear turbid, and there will be the pathological changes of "clear yang under, then give birth to diarrhea".^[33] Yangming and Taiyin on the meridians are the exterior and interior of each other, the intestines reach the stomach and the heart, the spleen collaterals and stomach are injected into the heart, and the meridians are connected, which fully reflects the close meridian relationship between the spleen and the large intestine.

3. Summary

As an end-stage manifestation of a variety of cardiovascular diseases, heart failure is a disease that leads to myocardial systolic and (or)diastolic dysfunction due to a variety of reasons. It is also a disease involving cardiovascular, digestive, neuroendocrine, kidney and immune system abnormalities. Through the research of modern medicine, it is found that the main pathogenesis revolves around the mechanism of sympathetic-renin-angiotensin-aldosterone system, immune inflammatory response, myocardial remodeling, neuroendocrine mechanism and so on. These mechanisms affect the pathogenesis and prognosis of heart failure. With the in-depth study of the mechanism of heart failure, it is found that intestinal flora is closely related to the occurrence and course of heart failure, which opens a new direction for the treatment of heart failure. Through the exploration of the basic theory of traditional Chinese medicine, it is found that the heart is connected with the spleen and intestinal meridians, and the physiology and pathology are interrelated, which also provides a theoretical source for the treatment from the spleen and the intestine. Combined with the knowledge of modern medicine, modern doctors fully excavate the relationship between traditional Chinese medicine and modern medicine, and put forward the theories of "heart-spleen-intestine", "treatment of psychological spleen" and "intestinal axis", which make up for the lack of understanding of heart failure in traditional medicine. This paper expounds the connotation of the theory related to the five internal organs more specifically, and can take this opportunity to provide more methods for the prevention and treatment of heart failure by the combination of traditional Chinese and western medicine. It also opens up new ideas for the excavation of more therapeutic targets and the research and development of new drugs.

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