

Research Progress of Correlation between Regulating Intestinal Microflora Disorder and Heart Failure in TCM and Western Medicine

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Abstract: Intestinal flora is a commensal microbial community in the intestinal tract of human body. many studies have proved that the imbalance of intestinal flora is closely related to many diseases. The correlation between heart failure and intestinal flora is a hot topic in medical research nowadays. The imbalance of intestinal flora is closely related to the occurrence and development of heart failure. A large number of studies have shown that TCM treatment can play a role in the treatment of heart failure by restoring intestinal homeostasis and regulating the types of flora and the level of metabolites, which has been widely used in the prevention and treatment of heart failure.

Keywords: Intestinal flora; flora imbalance; heart failure; treatment of traditional Chinese and Western medicine

1. Introduction

Heart failure (HF), is a group of syndromes caused by ventricular filling and/or impaired ejection capacity due to various heart structural or functional diseases, with cardiac output unable to meet the needs of body metabolism, insufficient blood perfusion of organs and tissues, and blood stasis of lung and/or systemic circulation. The clinical manifestations are mainly physical activity limitation and edema caused by dyspnea and weakness ^[1]. With the growth of age, the prevalence of heart failure increases rapidly. The prevalence of people over 70 years old rises to more than 10%. The four-year mortality rate of heart failure reaches 50%, and the one-year mortality rate of patients with severe heart failure reaches 50%. It is the end-stage manifestation of cardiovascular disease and the main cause of death. Modern research indicates that intestinal flora plays an important role in the occurrence, development and treatment of heart failure, and "intestinal hypothesis of heart failure" has been proposed ^[2]. Traditional Chinese medicine (TCM) is a unique theoretical system of the Chinese nation. In its traditional theory, the viewpoints of "holism" of zang-fu organs and "the exterior-interior relationship between heart and small intestine" have something in common with the role of intestinal microorganisms. In the literature of traditional Chinese medicine, heart impediment, heart cough, heart water, heart distension, heart failure, heart failure and other diseases are related to heart failure ^[3]. This study summarizes the clinical and basic research progress in the treatment of heart failure by regulating the intestinal flora in traditional Chinese medicine in recent years, in order to provide new ideas and theoretical basis for the prevention and treatment of the disease.

2. Overview of intestinal flora

The intestinal tract is the largest digestive, excretory and immune organ of the human body, as well as the largest bacterial reservoir and endotoxin pool, with about 100 trillion microorganisms stored therein, which constitute the intestinal flora ^[4]. During the evolution of intestinal flora, a symbiotic relationship was formed with the host cells. The intestine provides a good living environment for the growth and reproduction of microorganisms, and the intestinal flora plays an important role in maintaining the homeostasis, nutritional metabolism and health of the intestinal environment ^[5]. Studies have shown that the intestinal flora before birth is sterile. At birth, infants obtain the initial microflora from the mother's vagina and feces, which is mainly composed of Lactobacillus and Bifidobacterium, and the intestinal flora is basically formed by the age of 2 years old. Since then, the

number and type of intestinal flora are increasing, and it reaches a steady state in adulthood [6]. The intestinal flora is affected by age, gender, diet, lifestyle, antibiotic use and other factors, and the intestinal flora of the normal population is in dynamic balance with the human environment. At present, the main effects of intestinal flora recognized in clinical practice include: (1) Natural biological protection barrier: The intestinal anaerobes mainly composed of Bifidobacterium can form a natural biological barrier on the intestinal surface to resist the invasion of pathogenic bacteria and bacteria [7]. (2) Regulate the nutrition metabolism of the body. The intestinal flora is an important physiological function for regulating the intestinal tract, and the carbohydrate in the body is the main energy source for host cells and the intestinal flora. When the host cells cannot normally digest the polysaccharide and cellulose in food, they need to be degraded under the assistance of the intestinal flora to effectively regulate the blood glucose and lipid levels of the body, and provide the basic energy for the body [8]. (3) immunoregulatory effect, intestinal anaerobes can enhance the immune ability and non-specific immune ability of the body by activating the activity of phagocytes of the body [9].

3. The correlation between intestinal flora imbalance and heart failure

In the current research, people's understanding of the pathological and physiological mechanism of heart failure has changed significantly. It is believed that heart failure is not only a hemodynamic disease, but also involves multiple system disease states in metabolism, neuroendocrine and inflammation. Some basic studies have shown that changes in the composition of the intestinal flora and its metabolites are related to the occurrence and development of heart failure [10].

3.1. Intestinal flora imbalance

The latest evidence indicates that the intestinal flora of patients with heart failure is different from that of healthy people. Pasini [11] et al. confirmed that the number of intestinal pathogenic bacteria in patients with HF, such as Salmonella, Campylobacter, Shiga, Yersinia, Candida and other foreign bacteria was increased, while the number of native bacteria, such as Bifidobacterium and lactic acid bacteria was decreased. Moreover, the age, gender and body mass index were not statistically significant compared with those of the healthy control group, suggesting that patients with HF had dysbacteriosis [12]. 16S rRNA gene sequencing showed that the number of Actinomyces and Bifidobacterium was increased, while the number of Macromonas was decreased in patients with heart failure. Metagenomics and metabolomics analyses have revealed that the basic characteristics of the flora changes in patients with chronic heart failure are the decrease of *C. pratense* and the increase of active rumen cocci [13]. Bifidobacterium, Lactobacillus and Bacteroides are beneficial bacteria in intestinal flora and play an important role in body health. When HF occurs, its balance is damaged and the number of flora is significantly reduced, which is closely related to the severity of the disease. At the same time, the number of intestinal pathogenic bacteria such as Escherichia coli and yeast-like fungi in the patient was significantly increased, which was positively correlated with the levels of hs-CRP and BNP, and negatively correlated with LVEF, further promoting the deterioration of the disease. Therefore, the imbalance of intestinal flora in patients with HF is closely related to the level and condition of inflammatory response [14].

3.2. Increased permeability of the intestinal barrier and endotoxin translocation

Patients with heart failure not only have an imbalance of the intestinal flora, but also have increased permeability of the intestinal barrier and endotoxin translocation. Under physiological conditions, there is a layer of mucosal barrier between the intestinal contents and intestinal tract of human body, which is mainly composed of mucus secreted by intestinal epithelial cells and connexins tightly connected at the top of epithelial cells, to prevent intestinal epithelial cells and immune cells from directly contacting bacteria in the intestinal tract and inhibit inflammation and infection [1]. In the case of heart failure, the body will adjust the blood distribution throughout the body to ensure the supply of vital organs, of which intestinal ischemia and hypoxia occur earliest, and intestinal mucosal structure will suffer from ischemia-reperfusion injury. Patients with heart failure will have increased carbon dioxide pressure in gastric mucosa. Even in the condition of low-level activity, the weakened intestinal wall circulation and microcirculation disorder of patients will lead to intestinal mucosal edema and malabsorption, further resulting in weakened immune defense function and weakened resistance to bacterial adhesion, which is conducive to the migration of bacteria and toxins to extra-intestinal tissues and organs [15]. Endotoxin is a lipopolysaccharide (LPS) present in the cell wall of Gram-negative bacteria, which contains a hydrophilic polysaccharide moiety and a hydrophobic lipid A. The decline of intestinal barrier function results in the migration of large amount of endotoxin in the intestinal lumen to the extra-intestinal tissue, which is called endotoxin translocation. Endotoxin can cause submucosal edema, necrosis of the

cells at the top of the intestinal villi, and increased intestinal permeability, thereby destroying the function of the intestinal barrier. Bacterial translocation may be controlled in some cases, but endotoxin can still pass through the "leaky" intestinal mucosa, causing the activation of inflammation and the release of cellular mediators [16]. Microbial and lipopolysaccharide levels in the blood have been considered markers of impaired intestinal barrier.

3.3. Metabolites of Intestinal Microflora

The known intestinal metabolites related to heart failure include trimethylamine oxide (TMAO), short-chain fatty acids (SCFAs), and bile acids. The intestinal flora has been shown to participate in TMAO formation by producing trimethylamine (TMA), which, once in the blood, is transported to the liver and then converted to TMAO under the catalysis of flavin monooxygenase (FMO) [17]. Plasma TMAO levels were elevated in patients with heart failure and the E. coli to Shiga ratio was positively correlated with blood trimethylamine oxide levels in patients with compensated heart failure, indicating a correlation between intestinal flora imbalance and blood trimethylamine oxide levels [13]. In a 5-year follow-up of 720 patients with stable heart failure, the mean TMAO of enrolled patients was 5.0 μ mol/L, which was higher than that of patients without heart failure (3.5 μ mol/L; $P < 0.001$). Patients with higher plasma TMAO levels had a 3.4-fold increased risk of death. After adjusting for traditional cardiovascular risk factors and BNP, an increase in TMAO levels still predicts an increase in the 5-year mortality rate [18]. Another key metabolite of intestinal flora, short-chain fatty acids (SCFAs), is the main energy source of the intestine. SCFAs not only maintain the stability of the intestinal barrier, but also regulate the immune system, improve the microenvironment of the intestinal mucosa, and maintain the normal function of the intestinal mucosa, playing a defense function against the invasion of pathogenic bacteria and harmful substances [19]. In addition, SCFAs can be recognized by specific host receptors and improve the prognosis of heart failure by regulating host blood pressure and inhibiting ventricular remodeling [20]. Short-chain fatty acid-producing bacteria in the intestines of patients with heart failure are significantly reduced. 16s RNA analysis of intestinal microorganisms showed a significant reduction in SCFA-producing bacteria in intestinal microorganisms of patients with heart failure, e.g., *Eubacterium rectal*, *Dorea Longicatena* [21,22]. Short-chain fatty acids play an important role in the regulation of inflammation and the maintenance of the integrity of the intestinal barrier. SCFA can exhibit multiple effects [23], which can exert anti-inflammatory and pro-inflammatory effects on macrophages, and induce the release of inflammatory mediators such as nitric oxide (NO), IL-6, and IL-12 by activating intestinal macrophages, thereby preventing myocardial hypertrophy and fibrosis [24]. The metabolism of bile acids depends on the action of intestinal flora. The composition and content level of bile acids in patients with HF are significantly changed compared with those in the normal control group, especially the change of secondary bile acid spectrum. Specific secondary bile acids (such as ursodeoxycholic acid) can inhibit the inflammatory response caused by NF-KB by regulating FXR bile acid receptors. Studies have also shown that targeted treatment of FXR can reduce myocardial cell apoptosis and fibrosis, thereby improving the prognosis of heart failure [25].

4. Exploration of TCM theory of heart failure based on intestinal flora

4.1. Heart-spleen correlation

The concept of holism and the theory of the integration of five zang-organs are the important theory and essence of TCM, and the correlation between heart and spleen is an important part of the theory of the integration of five zang-organs. It is mentioned in lingshu meridian that "the pulse of the Taiyin of the spleen foot, the branches of which are connected from the stomach to the septum and into the heart.....the great collateral of the spleen, is called big bag, which comes out three inches into the axilla and spreads over the chest and hypochondrium". It is recorded in Su Wen Ping Ren Qi Lun that "the great collateral of the stomach is named Xuli, which runs through the septum and collaterals lung. It comes from under the left breast, so its movement should be based on the hand, and the pulse should be based on qi". The spleen is located in the middle energizer and serves as the hub of qi movement of the whole body. It is recorded in Su Wen Bielun of Meridians that "the food qi enters the stomach and disperses the essence into the liver, while the yin qi flows into the tendons. When the food qi enters the stomach, the turbid qi will return to the heart and the pathogen will be transferred to the pulse. The meridian qi flows through the meridians and is transferred to the lung, which faces hundreds of meridians and is used for seminal emission. Mao pulse combines with essence and moves qi to the fu. The spirit of the government is clear, so it will remain in the four zang-forces, and the qi will be weighed ". According to zang-fu theory, the heart stores spirit, which is the sovereign of five-zang and six-fu, and has the function of commanding the physical and psychological activities of the whole body. The spleen, however, controls the transportation and transformation of qi and blood, serving as the

source of biochemical transformation of qi and blood, as well as providing the material basis for the sovereign function of the heart. It indicated that the normal operation of spleen could promote the smooth flow of other organs, facilitate the coordination of qi and blood, and prevent the invasion of pathogenic factors [3]. The heart and spleen are separated in anatomical position by only one layer of diaphragm, which is in similar position. They are closely related through the meridian system. It is recorded in lingshu meridian that the branches of spleen meridian of foot Taiyin were connected with heart meridian of lesser yin of hand "from stomach, from diaphragm to heart". "Miraculous pivot, the don't" "foot taiyin is, up to the thigh, in yangming. And don't all line, knot in the pharynx, penetration of the tongue ... Hand less Yin is, don't into the Yu Yuan axillary between two tendons, belong to the heart, walk on the throat, out of the surface, eye inner canthus ". It could be seen that the difference between the two meridians met at the throat, further connecting the heart and spleen. Combined with the running of meridians and collaterals, it was characterized by the intersection of yin and yang, which resembled an endless loop, thus laying a more adequate foundation for the related theories of heart and spleen" [26]. Therefore, it indicates that the relevant theories of heart and spleen can guide the research on the relationship between intestinal flora and heart failure from the perspective of meridians and collaterals in traditional Chinese medicine.

Studies have found that in the human intestinal micro-ecological system, the normal flora can produce a variety of enzymes and participate in the digestion and absorption of nutrients [27]. If the normal community structure of the intestinal flora is changed, symptoms such as gastrointestinal discomfort will occur, and related intestinal diseases will continue to occur over time, which are consistent with the clinical manifestations of spleen deficiency syndrome in traditional Chinese medicine [28]. Spleen deficiency syndrome is a common syndrome in TCM clinical practice, and its main manifestation is digestion and absorption dysfunction, accompanied by systemic qi deficiency. Studies have found that spleen deficiency syndrome is closely related to the changes of intestinal flora [29]. Studies have found that Bifidobacterium in feces of patients with diarrhea due to spleen deficiency is significantly reduced, and the number of Bifidobacterium in feces is significantly increased after treatment with invigorating spleen. Animal experiments showed that the spleen deficiency mouse model prepared with Radix et Rhizoma Rhei decoction also had significant microecological imbalance, and the intestinal Lactobacilli and Bifidobacterium were decreased to different degrees [30]. Animal experiments showed that the mouse model of spleen deficiency constipation could be established by decocting Folium sennae in water. The total number of intestinal microorganisms after gavage was significantly lower than that in the normal group, and the E. coli and lactic acid bacteria were significantly increased, proving that the balance of intestinal microecology in the mouse model of spleen deficiency constipation was damaged to a certain extent [31].

4.2. Heart and small intestine exterior-interior

The heart and small intestine communicate with each other and collateral with each other on the meridians and collaterals to form the exterior-interior relationship. It is recorded in lingshu meridian that "the pulse of heart and hand with less yin originates from the heart and goes out to belong to the heart system and the lower diaphragm collaterals and small intestine ...", "the pulse of small intestine and hand with greater yang originates from the end of little finger and enters the deficiency basin to collateral the heart and travels down the pharynx to reach the stomach, which belongs to the small intestine." "Su Wen Gu Kong Lun" said: "Those who supervise the pulse, ... enter the collateral brain, ... penetrate the heart." Lingshu meridian said: "The pulse of the sun is sufficient, and the straight pulse enters the collaterals from the top", "The pulse of the yin and kidney is insufficient, and the ridge (the ridge leads to the brain) belongs to the kidney, and its branches exit from the lung and enter the collaterals and are injected into the chest". It is stated in Su Wen Zang Qi Shi Lun that "for patients with heart disease, pain in the chest, fullness of the hypochondrium, pain in the hypochondrium, above the back and shoulders and between the nails, and pain in the two arms". From the perspective of clinical symptoms, the painful parts of patients with heartache tend to radiate to the scapular region, which is very consistent with the running paths of small intestinal meridians. Small intestinal diseases are often accompanied by physical and mental diseases such as depression and anxiety. Studies have confirmed that small intestinal diseases can be transmitted along the meridians and collaterals, leading to the dysfunction of the heart in governing spirit. Many studies have shown that the trends of meridians and collaterals in multiple meridians, such as the governor vessel, manual Taiyang (GV 16), and foot Yangming (GV 20), are interconnected, and together they construct the meridian network system associated with the connection of the heart with the small intestine in the human body [28-29]. The exterior-interior relationship between the heart meridian and the small intestine meridian determines their physiological and pathological connections. The heart and small intestine physiologically function with each other. "Classic of Difficulties" reads: "Heart camp, lung guard, Yangqi traffic, the former residence on the; Large intestine, small intestine, Yin qi, former residence in the next, so a far cry from also ". On the one hand, the function of "heart governing blood

vessel" is based on the sufficiency of "heart yin" and "heart yang", and the combination of the two plays a role in promoting the small intestinal mass transfer through the meridian connection. On the other hand, the small intestine mainly receives the exuberant nutrients and secretes away the pure and turbid to realize the digestion and absorption of the human body as well as the downward transmission of the dross to the large intestine and bladder. The normal function of the small intestine is an important condition for harmonizing blood vessels, nourishing the five internal organs, and draining the dross. The heart and small intestine interact pathologically. "On the Causes and Symptoms of Diseases": "those who suffer from excessive salivation after heartache and stop drinking take advantage of the collaterals of the heart; those who stop drinking will behave like water and liquid ... The small intestine and the internal organs of the heart will also absorb the moisture descending into the small intestine to urinate, so there is no need to stop drinking in the heart collaterals ... If the multiplication of cold and heat causes the internal organs to be irregular, and the drinking of body fluid and water stops accumulating, the upper part is forced by the heart to make the heart qi unable to communicate, so the pain will be excessive salivation". According to the provisions, if the normal function of the small intestine "saturated with urine" is affected, it will lead to dysfunction of transmission. The production of nutrient substances is reduced, so that they cannot provide the sustenance and supply for the normal blood vessels. On the one hand, it causes the normal blood vessels to promote the decline of blood function, and on the other hand, it causes the state of qi and blood deficiency in the body, leading to the slowdown of blood movement, and eventually blood stasis. If the function of "clearing away turbidity" in the small intestine is out of control, the ascending and descending of "turbid" substances will be out of control, and those who are clear will not ascend, which will lead to diarrhea, while those who are turbid will not descend, which will produce pathological products such as phlegm and water-dampness, and phlegm and blood stasis will lead to dishonor of heart blood and depression of heart yang ^[20].

5. Research on the treatment of heart failure with traditional Chinese medicine based on the regulation of intestinal flora

The important relationship between heart and spleen has been expounded as early as in Internal Classic and Classic of Difficulties. For example, it is mentioned in the Plain Questions on Yin and Yang Correspondence Theory that "heart begets blood, and blood begets spleen". "Su Wen Yu Ji Zhen Zang Lun Pian" also mentioned: "The five zang-organs are nourished by qi from their organs ... The heart is nourished by qi from the spleen and transmitted to the lung. Qi is given up to the liver and ends up in the kidney. Grant gas in the spleen, grant gas in my son also ... ". Spleen, stomach and five elements belong to soil, while heart and five elements belong to fire. Heart and spleen are related. In addition, Yin and Yang of heart and spleen are interlinked, and qi and blood are mutually complementary. The related theories of heart and spleen came into existence in Qin and Han Dynasties, flourished in Song Dynasty, matured in Ming and Qing Dynasties, and gradually improved in modern times. On the treatment of chest stuffiness and heartache, Professor Deng Tietao, a master professor of Chinese medicine, proposed that "the key of tonifying heart and qi is to invigorate spleen" and "phlegm and blood stasis are related", and emphasized the related theory of heart and spleen, pointing out that the dysfunction of spleen and stomach transportation and transformation caused by improper diet, internal injuries caused by seven emotions, and aging and tonifying deficiency existed in dampness and turbidity, which gathered to produce phlegm, which grew into blood stasis over time, leading to chest stuffiness and stroke. Deng Lao used modified Wendan Decoction to treat coronary heart disease and obtained the effect of replenishing qi and removing dampness. The practice proved that the effect was quite good. The common pathological mechanism for the occurrence and development of cardiovascular and cerebrovascular diseases is "phlegm and blood stasis correlation". The dysfunction of spleen and stomach is the key, and it is closely related to the function of intestinal flora. Specifically, it refers to the production of TMA when eating fatty, sweet, and greasy products rich in choline under the related action of intestinal flora. TMA is considered as the biological marker of "phlegm and blood stasis". TMA enters blood and is converted into TMAO in liver, which promotes the progression of atherosclerotic plaques, activates platelet aggregation, promotes the formation of arterial thrombosis, and eventually leads to the occurrence of atherosclerotic diseases. These are the pathological bases of blood vessel occlusion caused by "phlegm and blood stasis mutual junction". Professor Lu Zhizheng is good at using the methods of regulating spleen and stomach to treat chest impediment and heartache in clinical application, including invigorating spleen and nourishing blood, warming yang in principle, enlivening spleen and resolving dampness, invigorating spleen and eliminating phlegm, and the curative effect is significant. Modern research has also shown that drugs related to the regulation of spleen and stomach can prevent atherosclerosis by promoting gastrointestinal digestion and absorption function, improving energy and material metabolism, reducing vascular pressure by regulating lipid metabolism, and reducing intimal damage and lipid deposition by improving lipid peroxidation damage. It can be seen that based on the "intestinal flora", it is a feasible way to explore the effective treatment of cardiovascular diseases from the spleen and stomach. At the same time, increasing evidence also

shows that intestinal flora is involved in the cardiovascular pharmacological effects of Chinese medicine. For example, the study has revealed that the efficacy of Shenling Baizhu Powder in the treatment of cardiovascular disease of spleen deficiency syndrome is related to the structural changes of intestinal flora. Ding Weijun et al. established the spleen deficiency mouse model by gavage with Radix et Rhizoma Rhei and given Shenling Baizhu Powder for treatment. The results showed that Shenling Baizhu Powder could significantly increase the content of intestinal Bifidobacterium, reduce the number of Enterococcus and Escherichia coli, and foster probiotics. They indirectly inhibited the opportunistic pathogens and pathogenic bacteria, and played a good role in regulating the recovery of the dynamic balance of intestinal flora.

6. Summary and prospect

The pathogenesis of heart failure is complex, and the mortality and re-hospitalization rate are high, which are still difficult problems in the medical field. In recent years, with the deepening of research on intestinal flora, the correlation between heart failure and intestinal flora has been gradually found, which provides a new idea and direction for the treatment of this disease. Due to the blood stasis of gastrointestinal circulation, there are changes in the morphology and function of the intestinal tract as well as changes in the composition and metabolites of the intestinal flora in heart failure. The continuous aggravation of heart failure can further aggravate the imbalance of intestinal function and the disorder of intestinal flora, thus forming a vicious circle. Chinese medicine can cut off the vicious circle in many ways, restore the steady state of intestinal microorganisms, and alleviate the metabolic disorders and inflammatory reactions caused by the imbalance of intestinal flora. Due to the advantages of multiple targets and low toxicity, Chinese medicine has been widely used for the prevention and treatment of heart failure. Although more and more studies have confirmed that Chinese medicine can treat heart failure by regulating the intestinal flora, most of them remain in the phenotypic studies and lack of further exploration of the specific mechanism. At the same time, due to the complexity of Chinese medicine components and the diversity of intestinal flora, the interaction between them also needs further study. It is hoped that the advantages of traditional Chinese medicine can be continuously exerted in the future to provide a more effective method for the treatment of heart failure [32].

Acknowledgement

Shaanxi Provincial Science and Technology Plan Project (2021JM-481).

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