

The Exploration of the Relationship between Intestinal Flora and Hypertension based on "heart and small intestine"

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Abstract: "The heart and the small intestine are in sympathy with each other" is one of the classical theories in Chinese medicine, which believes that the heart and the small intestine are in sympathy with each other, and the internal organs are in sympathy with each other, with physiological correlation and pathological correlation, therefore, in terms of treatment, there are methods to treat the internal organs for diseases of the organs, to treat the internal organs for diseases of the organs, and to treat the internal organs together. This theory is in line with the modern medical research that hypertension is related to the intestinal flora. It is found that the occurrence of hypertension will cause changes in the structure, diversity and richness of the intestinal flora, and similarly, the metabolites produced by the intestinal flora will in turn affect the development of hypertension. Therefore, this article intends to discuss the TCM connotation of "the heart and small intestine are in harmony with each other", the TCM etiology and pathogenesis of hypertension, and the relationship between hypertension and intestinal flora, in order to provide new ideas for the regulation of intestinal flora in TCM to prevent and treat hypertension.

Keywords: Heart and small intestine; Hypertension; Intestinal flora; Chinese medicine

1. Introduction

Hypertension is one of the most common chronic diseases, the pathogenesis of which is still unclear, and it is one of the most dangerous public health problems. Epidemiology shows that 245 million people over 18 years of age in China have hypertension, while the awareness, treatment and control rates of hypertension are 46.9%, 40.7% and 15.3% respectively, which are still at a low level overall [1]. The overall awareness, treatment and control rates are still low. Poorly controlled hypertension is associated with damage to the heart, kidneys, blood vessels and other important target organs, and is characterised by high disability and mortality rates. With recent breakthroughs in macrogenomics and metabolomics, the development of hypertension has been found to be closely related to metabolic disorders of the intestinal flora [2]. In addition, the theory of "heart and small intestine are in harmony with each other" in Chinese medicine can explain the relationship between hypertension and intestinal flora to a certain extent, and provide new ideas and methods for the prevention and treatment of hypertension.

2. Connotation of "the heart and small intestine are in sympathy with each other"

The discussion of "heart and small intestine" was first mentioned in the "Spiritual Pivot - Benluo": "The heart is in harmony with the small intestine, and the small intestine is the internal organ that receives the fullness of the body." It shows that the heart and the small intestine are one organ and one internal organ, and that they are mutually complementary in physiology and affect each other in pathology, and that they are interconnected through the meridians, forming a one-to-one correspondence between the genera and the ligaments. The Ling Shu - Pulse Classic says: "The pulse of the Heart Hand Shao Yin starts in the Heart and goes down to the diaphragm and contacts the Small Intestine" "The small intestine hand Sun's vein starts at the end of the little finger and enters the absence of the basin, lining the heart", the Sun meridian and the Shao Yin meridian are mutually connected, through the branch veins and other meridians together to complete the twelve

meridians The heart is connected to the small intestine and even to other internal organs at a deeper level. This is in line with the statement in *Su Wen - Zang Qi Fa Shi Lun*, "When the heart is ill, there is pain in the middle of the chest, fullness in the branches, pain under the dorsum, pain between the shoulder nails, and pain within the two arms", which also reflects the characteristics of the connection between the heart and small intestine meridians [3]. It also reflects the fact that the heart and small intestine meridians are connected.

Physiologically, the heart and the small intestine complement each other. The heart is the sovereign's official, residing in the upper jiao of the body, and the five elements are fire. In addition, the heart is the master of the blood vessels reaching the small intestine, so the heart can dominate the physiological rhythm and functions of the small intestine, ensuring that the function of the small intestine in separating the clear from the turbid and metabolizing water and fluids is normal. On the other hand, the small intestine is a fire internal organ, which receives all kinds of water and grain essence and transforms it into qi and blood for distribution throughout the body, of which the thick part is transferred to the heart via spleen qi and transforms blood to feed the heart vessels, and transforms the dregs into the large intestine and bladder to form two stools, so as to maintain the digestion and absorption of food and normal water and fluid metabolism of the human body, which embodies the physiological characteristics as stated in the *Essence of Medical Scriptures* [4]. The physiological characteristics of the small intestine are as stated in the *Essence of Medical Scriptures*: "The small intestine is full of food, which is the Yang quality, drink is the main transformation of gas, food is the main transformation of blood, food in the small intestine are transformed into liquid, in order to out of even outline, so up to the heart and blood, so the small intestine is the heart of the internal organs, is the heart to take materials." The *Medical Principles Xu Yu* states: "The small intestine is the heart's capital, the heart is red in colour, so the small intestine is the red intestine, which leads the heart's fire and turbid gas downwards, but does not make it dry up in the Hua Gai, which is also called the capital of tolerance." This is also a reflection of the mutual use of the two.

Pathologically, the heart and the small intestine interact with each other. The *Treatise on the Origin of Diseases* says: "The heart is the master of blood, and is united with the small intestine. If there is heat in the heart, it is knotted in the small intestine, hence the blood in the urine." In the Ming Dynasty, Yu Tuan's book *"The Life of the Crowd"* [5] says that "If there is fire in the heart, the heat will remain in the small intestine for a long time, and then the urine will become constipated." It shows that if the heart fire is strong and spreads to the lungs, the lungs are the heavenly curtain and are on the cold side, promoting the downward transmission of heart fire to the small intestine, which will lead to short, red urine, stinging pain and urine loss, and other symptoms of real heat in the small intestine; and real heat in the small intestine can also be inflamed upwards in the heart through the meridians. In the *"Zhongzang Jing - On the Method of the Evidence of the Reversed Pulse of the Small Intestine for Deficiency, Cold, Heat, Life and Death"*, it is also mentioned that "if the small intestine is solid, heat is injured, and heat causes sores in the mouth" [6]. The *"Chinese Collection Sutra"* also mentions that "if the small intestine is solid, heat is injurious, and heat causes sores in the mouth. The heat of the small intestine can also be seen in symptoms of the heart such as heartburn, panic and insomnia, as in Wang's *Medical Cun - Volume 8*: "In the organs, the heat of the small intestine moves upwards, so it cannot sleep". In addition, if the heart is not warmed by the yang, the small intestine is cold, and the transmission and transformation of things are out of order, it is unable to differentiate between the clear and turbid, and to distribute the essence to the spleen to transform blood. Therefore, the *Pulse Classic* says: "If the left hand is deficient in both yin and yang before the left inch and mouth and the left hand is deficient in both the Shao Yin and the Sun meridians, the disease is bitter and cavernous, the extremities are cold and the intestines are verminous."

3. The link between the theory that the heart and the small intestine are in sympathy with each other and hypertension

Blood pressure is formed by the lateral pressure of blood against the walls of the blood vessels when the heart contracts to eject blood on the basis of an adequate volume of circulating blood. In Chinese medicine, *"Suwen - Plankton"* says: "The heart is the master of the blood vessels of the body", and heart qi drives and regulates the pulsation of the heart and the expansion and contraction of the veins, suggesting that blood pressure is closely related to the function of the heart as the master of the blood vessels. In the *Spiritual Pivot - Determining Qi*, it is said that "when the Ying Qi is congested, there is no way to avoid it, this is called the pulse", and when the Heart Qi is abundant, the blood is full, and the pulse channels are open, the pulse is gentle and strong. When the small arteries throughout the body have thickened walls and narrowed lumens for various reasons, the resistance to blood flow

increases, leading to a rise in blood pressure and hypertension, which corresponds to a "large and firm pulse" in Chinese medicine. The earliest explanation of this theory can be found in the *Spiritual Pivot - Theory of Distension* [7]. The Yellow Emperor said: How does the pulse, which should be at the mouth of the inch, become distended? Qibo said: The pulse that is large and firm and astringent is also distended. The Yellow Emperor said: "Where does the distension arise? How does it come about? Qibo said: the Wei Qi in the body also, always and the pulse, and follow the flesh, the line has a reverse, yin and Yang follow each other, so as to get the heavenly harmony, the five organs to change the beginning, the four seasons in order, the grain is transformed. Then the syncretic Qi in the lower, Ying and Wei stay stopped, the real evil attack each other, the two Qi fight each other, is combined and become bloated", where the description of "pulse bloating" is similar to the modern Western medical description of hypertension. The description of "pulse distension" is similar to the modern description of hypertension in Western medicine, while the distension of the pulse channels due to the disorder of the Ying and Wei and the Qi and Blood is considered to be the cause of "pulse distension" [8]. This is the cause of the distension of the veins.

In ancient times, various medical practitioners had different perceptions of hypertension, hence the different Chinese medical names for it, such as "vertigo" and "headache". In the *Su Wen - General Commentary on Deficiency and Actuality*, "Headache and tinnitus are the result of the blockage of the nine orifices, which is also caused by the intestines and stomach". Wang Bing of the Tang Dynasty commented that "when the intestines and stomach are blocked, the qi is not in order, and when the qi is not in order, the upper and lower parts of the body and the outer parts of the body win or lose each other, so the dizziness and tinnitus are not conducive to the nine orifices", stating that the "headache" is located in the upper part of the body, but the cause of the disease may be in the lower part of the intestines [9]. The explanation for this theory is that, firstly, from the meridian point of view, as the Hand Sun Small Intestine Meridian and the Hand Shao Yin Heart Meridian travel up to the head and face, "in the case of heart disease, the points of the small intestine must be taken to relieve it", the headache caused by hypertension should be taken from the above two meridian points to relieve its evil and solve its symptoms. Secondly, in terms of the internal organs, the small intestine has a normal function of differentiating between clear and turbid Qi, so that clear Qi moves up to the brain and turbid Qi moves down to the second yin, so that Qi and blood flow smoothly and the brain is clear and the mind is clear, then blood pressure can be stabilized.

Modern medical research shows that H.D cells in the upper part of the small intestine secrete vasoactive peptides, which can increase the secretion of small intestine and pancreatic juice, promote the digestion and absorption of small intestine, and vasoactive peptides can enhance myocardial contraction, enhance vasodilation, and thus lower blood pressure [10]. In addition, it has been found that vasoactive peptides are dispersed throughout the small intestine. It has also been found that T cells dispersed throughout the intestinal epithelial layer of the small intestine regulate metabolism and accelerate the development of cardiovascular disease, and experiments have shown that mice naturally deficient in these T cells have a significantly lower risk of developing hypertension, diabetes and atherosclerosis when fed a high-fat and high-sugar diet [11]. The risk of hypertension, diabetes and atherosclerosis was significantly reduced in mice fed a diet high in fat and sugar. In addition, S cells in the upper intestinal mucosa of the small intestine, the bulb of the duodenum, the jejunum and the ileum secrete glucagon, which increases cardiac output and has a direct dilating effect on the mesenteric and hepatic arteries [12]. It also has a direct dilating effect on the mesenteric and hepatic arteries. This provides strong evidence that the Chinese medicine theory of "heart and small intestine are in sympathy with each other" is closely related to hypertension.

4. Intestinal flora and hypertension

4.1. Environmental homeostasis of the intestinal flora

The intestinal flora (Gut Microbiota GM) is the largest microbial reservoir in the human body, consisting of approximately 100 trillion microorganisms and containing 100-1000 bacterial species, and is a special organ of the human body [13]. It is involved in the protection, metabolism, composition and function of the intestinal tract and is relatively stable in structure, but at the same time age, genetics, environment, health status and other factors can cause changes in the structure of the intestinal flora [14]. It is a special organ of the human body that is involved in the protection, metabolism, composition and function of the intestine. Studies [15] have shown that the intestinal flora interacts with the host through the intestinal mucosal epithelium and its good balance is maintained by restoring the structure of tight

junction proteins, up-regulating mucin genes and inhibiting the binding of epithelial cells to pathogenic bacteria, among other functions. In the presence of impaired cardiac function, intestinal wall oedema may reduce intestinal blood flow and consequently the structure of the intestinal mucosal epithelial barrier is disrupted and endotoxins enter the circulation, triggering an immune response leading to systemic inflammation, while evidence suggests that increased intestinal epithelial barrier permeability and inflammation are strongly associated with hypertension [16]. Maintaining a balance between flora and fauna may therefore reduce the incidence of cardiovascular disease to some extent. Researchers have divided the intestinal flora into nine phyla according to their natural properties, with the healthy adult intestine consisting mainly of the thick-walled phylum and the anaphyla phylum, which make up 2/3 of the flora and are usually dominant, while the phylum Actinobacteria, Aspergillus and Verrucomicrobia, although present in many people, are usually minor components [17]. A variety of bacteria and microorganisms inhabit the human gut in a symbiotic manner, and together they participate in physiological processes such as the body's immune response, metabolism, inflammatory response and endocrine regulation. The risk of hypertension is significantly increased when the intestinal flora is less abundant, less diverse and when the ratio of F. thick-walled to B. mimicus phylum (B) increases [18].

4.2. Correlation between intestinal flora and hypertension

Hypertension occurs due to a combination of different risk factors and host genetic and environmental factors. With the development of genomics and metabolomics technologies in recent years, more and more studies have shown that dysbiosis of the gut flora and metabolites of the gut flora play an important role in blood pressure control.

One experiment, using high-throughput sequencing studies of human and rat stool samples, found that the abundance and diversity of the gut microbiota was significantly reduced in hypertensive patients compared to healthy adults; similarly, the flora of the spontaneously hypertensive rat (SHR) group followed a similar pattern of poor biology with significantly reduced microbial abundance, homogeneity and diversity compared to the Wistar Kyoto rat (WKY) group [19]. In contrast, by transplanting hypertensive human donor faeces into germ-free mice, elevated blood pressure was observed to be transferred through the flora, further demonstrating the existence of a direct effect of GM on host blood pressure [20]. So, in what way does GM achieve its goal of affecting blood pressure. Some investigators [16] have proposed that Gut dysbiosis as a trigger for the development of hypertension may be caused by increased sympathetic tone in the gut, increased permeability of the intestinal wall and increased systemic inflammation, so it is thought that alterations in gut pathology and physiology cause dysbiosis of the intestinal flora, which in turn affects blood pressure. Probiotics have antimicrobial activity, enhanced intestinal barrier function and immunomodulatory effects through their actions on a variety of immune cells. Oral administration of probiotics expressing Ang(1-7) significantly increased circulating levels of peptides associated with improved microbiome diversity indices in aged rats, particularly the anti-inflammatory species Akkermansia muciniphila, which similarly affects the integrity of the intestinal barrier [21]. The above evidence suggests that GM may play a key role in the control of blood pressure homeostasis and that any changes and/or imbalances in flora composition could potentially lead to hypertension. So if studies find that there is an excess or reduction of a specific bacterium in hypertension, then tailored treatment could be administered to correct this imbalance, however, it has been shown that in animal models of hypertension and in patients with hypertension, there is no specific bacterium that is closely associated with hypertension, but rather the function of the entire gut flora is altered, so maintaining a balance between the flora is the principle of treatment for hypertension [22].

GM is involved in host metabolism to produce a variety of substances, with the main metabolites including short-chain fatty acids (SCFAs) and trimethylamine nitrogen oxides (TMAO). The various metabolites play different roles in the development of hypertension. Short-chain fatty acids (SCFAs) are an important class of signalling molecules produced by intestinal flora fermenting dietary fibre, of which about 90% are produced by bacterial fermentation in the colon and the rest by dietary intake of protein and other metabolites. They mainly contain acetic acid, propionic acid and butyric acid in a 3:1:1 ratio, and are not only energy substrates for the intestinal epithelium, but are also involved in regulatory functions [23]. Butyrate and acetate restore endothelium-dependent vasodilation of the aortic rings and also increase the bioavailability of nitric oxide (NO) thereby affecting blood pressure regulation [24]. Propionic acid was effective in reducing blood pressure, inflammatory response and cardiac injury in Ang II-induced hypertensive mice and restoring vascular endothelial function [25]. Butyrate is a single-chain fatty acid with anti-inflammatory properties and protective effects on the

cardiovascular system ^[26]. It may have beneficial effects by stimulating specific fatty acid receptors (FFAR), which produce direct vasodilatory effects, or by stimulating intestinal vagal afferent FFAR to induce pressure reduction in the parasympathetic pathway of the brain. Recent studies ^[27] have shown that a 2-3 fold increase in the concentration of butyrate in the colon produces significant hypotensive effects via afferent colonic-vagal signalling and GPR41/43 receptors. In addition, SCFAs also modulate inflammation in the intestinal and parenteral environment and show protective effects against hypertension by reducing inflammation and immune responses. Thus short-chain fatty acids and butyrate are considered to be key substances in maintaining intestinal health.

Another major group of metabolites of GM, trimethylamine nitrogen oxide (TMAO), is produced by the metabolism of choline, phosphatidylcholine. High levels of trimethylamine oxide in the arteries increase circulating cholesterol deposition and contribute to atherosclerosis. A Meta-analysis showed a dose-dependent relationship between circulating TMAO concentrations and risk of hypertension, with each 10 $\mu\text{mol/L}$ increase in circulating TMAO concentration associated with a 20% increase in the relative risk of elevated blood pressure ^[28]. TMAO directly constricts small arteries, sensitizes blood pressure to Ang II, and activates the ROS/CaMKII/PLC β 3/Ca $^{2+}$ pathway, enhancing Ang II-induced vasoconstriction and causing an increase in blood pressure ^[29]. In addition, blood pressure can be affected by impairing endothelial cell function. TMAO can induce dysfunctional self-repair of vascular endothelial cells and inhibit nitric oxide (NO) production, weakening the endothelium-dependent vasodilatory response induced by acetylcholine, resulting in increased blood pressure ^[30]. Tyrosine, also a GM metabolite, has the potential to alter sympathetic neurotransmitters, leading to sympathetic dysregulation and the development of hypertension ^[31]. In addition, metabolites of other intestinal flora are also involved to varying degrees in the development of hypertension ^[32].

5. Intestinal flora regulation in Chinese herbal medicine to intervene in hypertension

In modern medicine, hypertension is considered to correspond to "vertigo" in traditional medicine, based on its main clinical manifestations, and the understanding of its etiology and pathogenesis by ancient physicians is constantly evolving. Based on the principle that "all winds and dizziness belong to the liver", the treatment of dizziness is based on the theory of the liver, with methods to calm the liver, dredge the liver and calm the liver being used according to the pathogenesis. There are also medical sages who understand that "no deficiency makes dizziness", "no phlegm makes dizziness" and "long-standing illnesses enter the ligaments", and that clinical evidence should be balanced with supporting and tonifying deficiencies, drying dampness and resolving phlegm, and activating blood circulation and resolving blood stasis. Modern research has found that different herbal medicines can lower blood pressure by regulating the type, diversity and richness of intestinal flora and the metabolites that affect intestinal flora.

Tian Ma and Gou Tang is a representative formula for the treatment of dizziness and hyperactivity of the liver. Clinical observations have shown that combining Tian Ma and Hooked Vine with western medicine can effectively improve clinical symptoms and stabilize blood pressure levels in patients with hypertension ^[33]. The combination of Tianma and Hookwort was found to be effective in improving clinical symptoms and stabilising blood pressure levels in patients with hypertension. According to the modern 16SrRNA gene sequencing and metabolomics study, after the administration of Tianma-Choeten to a rat model of chronic migraine, the structure of the intestinal microbial community changed significantly, as evidenced by the increase in the relative abundance of *Bacillus* spp. and *Coccidioides* spp. and the decrease in the relative abundance of *Prevotella* spp. and *Shigella* spp. in rats ^[34]. It is suggested that Tianma Gastrodiae Drink can regulate the structure of bacterial flora, which may be one of the reasons for its treatment of hypertension. The treatment should be based on Zhang Xichun's Liver and Wind Quenching Soup to calm the liver and quench the wind, and nourish Yin and submerge Yang. Xu Xinghua ^[35] found that compared with the model control group, the systolic blood pressure, diastolic blood pressure and mean arterial pressure were significantly lower in each dose of Zhenhe liver and quench the wind Tang group through the study on intestinal flora in spontaneous hypertension; the abundance of *Aspergillus* phylum decreased, the relative abundance of lactic acid producing bacteria in the cecum and colon decreased, and the relative abundance of butyric acid producing bacteria increased significantly. In addition, it was also found that Zhenhe Liver and Quench Wind Soup could lower blood pressure by regulating gastrointestinal hormones and improving gastrointestinal dynamics ^[36].

If vertigo is caused by weakness of the spleen and stomach, loss of health and movement, accumulation of dampness and phlegm, blockage of phlegm and dampness, and loss of nourishment of

the clear orifices, Huanglian Wendan Decoction can be added and reduced to clear heat and dry dampness, resolve phlegm and move Qi. The mechanism of Huanglian Wendan Decoction in lowering blood pressure may be related to its ability to regulate intestinal flora, improve intestinal blood flow, inhibit inflammatory response, protect intestinal mucosa and reduce the risk of hypertension complications [37]. The mechanism may be related to the regulation of intestinal flora, improvement of intestinal blood flow, inhibition of inflammatory response, protection of intestinal mucosa, and reduction of the risk of hypertension. If the invasion of fire and heat causes disturbance of the qi of the internal organs, qi and fire rushing upwards, heat becoming toxic, burning fluid and injuring yin, and phlegm and toxins intermingling, treatment can be given to clear heat and detoxify the body, invigorate the blood and remove blood stasis. Baicalin, one of the main ingredients of Huanglian Decoction, can effectively inhibit Ang II-induced hypertension-related intestinal barrier damage, promote intestinal mucosal epithelial tight junction protein expression, and regulate intestinal flora [38]. It also regulates intestinal flora. He Kai [39] found that baicalin alkaloids, a major component of *Scutellaria*, could alleviate hyperlipidemia by mediating bile acid metabolism and intestinal microbiota, and conversely it could reshape the imbalance of intestinal microflora caused by high-fat and high-cholesterol diet. Ma Xiacong [40] divided randomly eight 12-week-old male hypertensive rats into a model group and a group with Huanglian Jiedu Decoction, and their bioinformatics were analysed by 16S rDNA sequencing. The results showed that Huanglian Jiedu Decoction may have an antihypertensive effect by increasing the flora diversity of hypertensive rats, decreasing the relative abundance of the pathogenic bacteria *Lactobacillus* spp. There is also evidence that Huanglian Jiedu Decoction regulates the secretion of vascular endothelial factor, which can increase the endothelial diastolic factor and at the same time have a decreasing effect on the contractile factor in rats, thus optimizing the endothelial function and having some effect on blood pressure [41]. Blood stasis is another important pathological factor in the prolonged illness of vertigo. Therefore, the treatment of vertigo with Blood Stasis is not only consistent with the pathological changes, but also supported by modern research evidence [42]. The study found that Blood Mansions and Stasis Free Decoction Granules can increase the diversity and relative abundance of intestinal flora and reduce the level of its metabolite TMAO, which has the effect of lowering blood pressure.

With the development of modern medicine, there is more and more evidence that Chinese medicine can achieve the purpose of treating hypertension through the regulation of intestinal flora, but there is still a lack of systematic research on the specific mechanism of action of various drugs, so in future studies, the deeper mechanism can be explored through classification and comparison to better guide clinical practice.

6. Summary

"Modern research has shown that changes in the stability of the intestinal flora and changes in the proportion of different metabolites have an impact on the development of hypertension, all reflecting the idea that the heart and small intestine are in sympathy with each other, which provides a new perspective on the treatment of hypertension from the intestinal organs. This provides a new perspective for the treatment of hypertension from the internal organs. Therefore, in future research, we should actively explore more beneficial bacteria in the human intestine, promote the production of beneficial intestinal metabolites and reduce the release of harmful metabolites through various therapeutic means, so as to maintain the dynamic balance of the intestinal flora. Chinese medicine is a cornerstone of TCM treatment. In future, the potential of Chinese medicine in the treatment of hypertension should be further explored in clinical practice, and a TCM treatment plan based on intestinal flora should be constructed, so as to bring greater value to the prevention and treatment of hypertension.

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