The Correlation Between Heart Failure and Gut Microbiome Metabolites

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Abstract
Heart failure (HF) is a global public health problem, with morbidity and mortality increasing year by year. The gut microbiome actively affects the physiological and pathological activities of the human body in a variety of ways. More and more studies have suggested a strong correlation between HF and gut microbiome metabolites. Our review summarizes the specific alteration of these metabolites and their connection to the progression of HF, aiming at considering new approaches toward regulating the gut microbiome and using its metabolic pathways to treat HF, potentially decreasing the morbidity and mortality of HF as well as improving prognosis.

Keywords: bile acid; heart failure; microbiome; short chain fatty acid; trimethylamine N-oxide

Introduction
Heart failure (HF) is the end-stage of various heart diseases. It is one of the main causes of disease incidence and death globally, with a prevalence of over 26 million people worldwide and resulting in more than 1 million hospitalizations annually in both the United States and Europe.1,2 Although great progress has been made in treating HF with cardiovascular medications, HF mortality is increasing yearly.3 In China, there are 13.7 million HF patients among adults aged ≥35 years.2 The mortality of HF patients in hospitals is 4.1%.4 Studies show the significant impact of inflammation and immune dysfunction on the pathogenesis of HF.5 The influence of the gut on the progress of HF is still under investigation. At present, there is quite a bit of evidence suggesting a significant role for the gut microbiome in the development of HF.6–8 The human intestine harbors more than 100 trillion microbes that aid the human body in operating multiple physiological activities, including energy metabolism, development of the neurological system, immune regulation, vitamin synthesis and absorption, and regulation of the normal function of the intestinal epithelial mucosal barrier.9–11 However, these microbes can also harm the human body and lead to the incidence and progression of cardiovascular disease (Table 1). Research has shown the value of increased trimethylamine N-oxide (TMAO), which is a gut microbiome metabolite, in predicting a poor outcome in both chronic and acute HF.12 Other research on the correlation between HF and gut microbiome metabolites is continuously emerging. However, these studies are all correlation studies which do not prove causality between the gut microbiome and pathogenesis of HF. This review will describe how gut microbiome metabolites, including TMAO, participate in the progress of HF and related interventions. (Fig. 1, Table 2).

Heart failure
HF is a complex clinical syndrome caused by any causes of abnormal changes in cardiac structure and function, resulting in the end-stage of various heart diseases.8 At present, HF is considered as a chronic and progressive disease, and the activation of the neuroendocrine system leads to pathological myocardial remodeling, which is the crucial factor in the occurrence and development of HF. In the field of modern medical, many drugs are being used, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers, aldosterone antagonists, and angiotensin receptor neprilysin inhibitor.13 However, current treatments target only a fraction of the putative pathophysiological pathways, the majority of patients and effective therapies to prevent HF are still lacking, suggesting that important pathogenic mechanisms are not addressed by current treatment modalities. The intestine is a complex micro-ecological system. More and more studies have shown that gut microbiome metabolites are expected to be an essential target for intervention of HF.

Gut microbiome
The gut microbiome refers to microbes that colonize the human gastrointestinal tract. There are at least 500 species of microbes,14 belonging mainly to five phyla (Actinobacteria,
Bacteroidetes, Firmicutes, Proteobacteria, and Verrucomicrobia) in the healthy adult gastrointestinal tract.\textsuperscript{15} The variation in gut microbiome species depends on multiple factors, including inheritance, environment, diet, and medications.\textsuperscript{14} The gut microbiome participates in digestion via two catalytic pathways: glycolysis and proteolysis.\textsuperscript{16} During digestion, short-chain fatty acids (SCFA), ammonia, amines, thiol, phenol, indole, and other compounds are produced, some of which are potentially toxic. In addition to digesting food, the gut microbiome regulates intestinal mucosa function, promotes maturation of immune tissue, inhibits the proliferation of pathogens,\textsuperscript{9} and regulates intestinal neuromuscular function.\textsuperscript{17} Studies have shown that impaired intestinal epithelial barrier function can increase intestinal permeability.\textsuperscript{7,16} Large amounts of endotoxins produced by the gut microbiome then enter the blood, inducing inflammation.\textsuperscript{8} Dysbiosis of the gut microbiome can tremendously change the intestinal and even the systemic immune system. In addition, the gut microbiome is closely related to the pathogenesis of gastrointestinal disease, cardiovascular disease, and other illnesses such as obesity, diabetes, and cancer. Specifically, gut microbiome metabolites have been confirmed as an important factor contributing to the occurrence and development of disease.\textsuperscript{19}

### Table 1

Summary of studies investigated links between gut microbiota and cardiovascular disease

| Alterations in gut microbiota composition | Alterations in gut microbiota metabolites | Proof of concept |
|------------------------------------------|------------------------------------------|-----------------|
| Heart failure                            | TMAO\textsuperscript{↑2,26}               | Gut permeability\textsuperscript{↑7} |
| Alterations in gut microbiota composition | TMAO was associated with heart remodeling and LVEF\textsuperscript{↑12,26} | |
| Atherosclerosis, coronary artery disease, and myocardial infarction | TMAO\textsuperscript{↑25} | Macrophage foam cell formation, and enhanced aortic atherosclerotic\textsuperscript{↑36} |
| Hypertension                             | TMAO\textsuperscript{↑25} | Circulating TMAO levels exhibited a positive correlation with atherosclerotic plaque size\textsuperscript{19} |
| Urolithiasis                             | TMAO\textsuperscript{↑25} | TMAO enhances platelet hyperreactivity and thrombosis risk\textsuperscript{19} |
| Hypertension                             | TMAO\textsuperscript{↑25} | Infusion of Ang II/TMAO associated with blood pressure\textsuperscript{↑48} |

CANS: cardiac autonomic nervous system; LVEF: left ventricular ejection fraction; SCFA: short-chain fatty acids; TMAO: trimethylamine N-oxide.

Figure 1. The role of gut microbiota in heart failure. ARGP: anterior right ganglionic plexi; CANS: cardiac autonomic nervous system; FMO: flavin-containing monoxygenase; IL: interleukin; NF-kB: nuclear factor-kappa B; TMA: trimethylamine; TMAO: trimethylamine N-oxide; TNF: tumor necrosis factor.
Candida present, the gut microbiome is imbalanced and presents are Salmonella, Campylobacter, Shigella, Yersinia, increase in microbiome changed greatly and the abundance of bacteria compared with healthy controls, the composition of the gut patients via 16S rRNA high-throughput sequencing and found lipopolysaccharide concentration is also higher. Pasini et al.7 the sigmoid mucosa, and their serum immunoglobin A-anti intestine blood Proteobacteria in HF patients of advanced age. Cui et al.23 and that intestinal perfusion decreases and intestinal barrier decreased cardiac output and sympathetic excitation cause vessel the gut in the pathogenesis of HF. It is widely believed that contribute to progression of HF, but the specific mechanism is still unclear. In a prospective observational study,28 researchers the correlation between dysbiosis and HF progression. Changes in the composition of the gut microbiome may contribute to progression of HF, but the specific mechanism is not clear yet. An increasing number of studies do suggest a role of the gut in the pathogenesis of HF. It is widely believed that decreased cardiac output and sympathetic excitation cause vessel contraction and redistribution of systemic circulation during HF, and that intestinal perfusion decreases and intestinal barrier function is impaired. Therefore, the endotoxins from the gut microbiome enter circulation and exacerbate systemic inflammation, further impairing intestinal barrier function and worsening HF.14 HF can also trigger congestion and edema in intestinal wall tissue, inhibiting intestinal absorption. Under these conditions, aerobic pathogens can colonize the gut more easily and harmful metabolites they produce move into circulation and worsen HF. Sandek et al.8 found that CHF patients with relatively low small intestine blood flow have higher bacterial colony concentration in the sigmoid mucosa, and their serum immunoglobulin A-anti lipopolysaccharide concentration is also higher. Pasini et al.7 found a 78% increase of intestinal permeability in patients with modest to severe CHF compared with healthy controls. However, this hypothesis does not reveal the correlation between the gut microbiome and HF pathogenesis in normal circumstances, or the correlation between specific taxa of the gut microbiome and the susceptibility to or severity of HF. Therefore, the dysbiosis of the gut microbiome in HF patients still requires further investigation to provide enough evidence to show a clear correlation.

**TMAO**

The gut microbiome metabolite TMAO is an important connecting point between cardiovascular disease and the gut microbiome. Choline, lecithin, L-carnitine, and other substances from red meat, eggs, diary food, and saltwater fish are all potential sources of TMAO.24 When these compounds enter the human body, they are metabolized to trimethylamine (TMA) by the gut microbiome, and TMA is then metabolized to TMAO by flavin-containing monoxygenase 3 after it reaches the liver via the portal venous system after absorption. TMAO is eliminated by the kidney.25

In Organ et al.’s research,26 mice were fed a diet supplemented with TMAO or choline and cardiomegaly and HF were induced by transverse aortic constriction. The result was increased circulating TMAO levels, pathological left ventricular dilation, decreased left ventricular ejection fraction, increased brain natriuretic peptide (BNP) levels, worsened pulmonary edema, myocardial fibrosis, and HF. Similarly, Li et al.27 employed transverse aortic constriction to induce cardiomegaly in Sprague-Dawley rats and observed that increased TMAO levels might correlate with increased intestinal permeability. In a concurrent in vitro experiment, the team discovered that TMAO can cause cardiomegaly in vitro after cardiomyocytes from new-born rats are treated with TMAO. In order to further verify the potential effects of TMAO in inducing cardiomegaly, they injected TMAO intraperitoneally into rats and found cardiomegaly in these rats and not in the control group. Animal model studies show high TMAO, whether through dietary choline or TMAO directly, can significantly enhance the remodeling of adverse chambers. However, the mechanism of action of TMAO within the heart is still unclear. In a prospective observational study,28 researchers found that serum levels of TMAO and its precursors choline and betaine (an oxidative product of choline) were all raised in 155 CHF patients. These levels were all associated with the clinical and hemodynamic severity of HF, but only TMAO can be used as a predictor of the risk of death in HF. Tang et al.12 followed 720 stable HF patients for 5 years and found a significant increase in fasting serum TMAO levels in HF patients compared with healthy controls; the increased TMAO levels also indicated a higher risk of death. Tang et al.29 quickly published another study measuring serum TMAO, choline, and betaine in 122 chronic systolic HF patients (left ventricular ejection fraction ≤35%) and they discovered that the raised levels of these indicators correlated with more serious left ventricular diastolic
function impairment and poor long-term outcome in chronic systolic HF. However, after adjusting heart kidney index, only increased serum TMAO correlated with poor outcome. Suzuki et al.36 studied the correlation between serum TMAO levels when acute heart failure patients were admitted and their outcomes, and discovered that TMAO was a univariable predictor of death. Schuetz et al.37 studied the correlation between TMAO and outcome for patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFrEF), and they found a predictive value of TMAO for death in HFrEF as opposed to HFrEF patients; the predictive value went beyond NT-proBNP. As before stated, a lot of studies indicated that TMAO can be used as a predictor of the outcome and risk of death of HF. Karlin et al.32 measured fasting serum TMAO in dogs with CHF secondary to degenerative mitral valve disease (DMVD), asymptomatic DMVD dogs, and healthy controls, and found a higher TMAO concentration in dogs with CHF secondary to DMVD. Zhou et al.38 conducted a prospective cohort study inspecting the prognostic value of TMAO in patients with CHF after myocardial infarction (MI) and found that TMAO was a valuable prognostic indicator of major adverse cardiac events in such patients. Salzano et al.39 studied the serum level changes of TMAO in HFrEF and HFrEF patients and found increased TMAO levels in both groups. Thus, they suggest that a combined assessment of BNP and TMAO levels could aid in risk stratification of HFpEF patients.

In order to investigate the mechanism of interaction between TMAO and HF, a great number of in vitro cell experiments have been conducted. Studies show that increased levels of circulating TMAO can cause foam cell aggregation and promote the formation of atherosclerotic plaque.35 Meanwhile, TMAO can alter calcium signaling to enhance the reaction of platelets.36 Therefore, TMAO can increase atherosclerosis and thrombosis, which are entwined in the upstream aetiologies that promote ischemic or non-ischemic HF. Studies have also shown that TMAO can induce inflammation and endothelial dysfunction via activating reactive oxygen species – thioredoxin-interactive protein – nod-like receptor family pyrin domain containing 3 inflammationosome.37 This gives rise to inflammatory cytokine release, inflammatory reactions, and endothelial dysfunction. Studies also suggest that TMAO upregulates pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, and worsens inflammatory reactions by activating the p65 nuclear factor (NF)-κB signaling pathway.38 These results suggest that TMAO might promote the development of HF by activating inflammatory reactions and accelerating endothelial cell dysfunction. There is research indicating that TMAO accelerates cardiomegaly and fibrosis via the TGF-β1/Smad3 signaling pathway.39 Some studies have observed the negative effects of TMAO on the contractility of cardiomyocytes in vitro.40 Other studies found that the ability of endothelial cells to both proliferate and migrate was impaired and cell aging was worsened after receiving TMAO, which might be related to suppression of sirtuin1 expression and increased oxidative stress.41 Endothelial cell aging would thus be induced through the p33/p321/Rib pathway. Yet more recent studies put forward a new mechanism through which TMAO induces T-tubule degeneration in mouse cardiomyocytes, promoting the translocation of JPH2 and remodeling of T-tubules, and ultimately leading to calcium-regulation dysfunction and impaired heart function.42 The results demonstrate that TMAO may promote the development of HF by accelerating endothelial dysfunction, including reducing endothelial self-repair activating the inflammatory response. In summary, the literature shows a strong correlation between TMAO and HF; however, the mechanism of interaction still needs more investigation.

**Short-chain fatty acids**

SCFAs are the main final product of dietary fiber passing through the gut microbiome. They include carboxylic acids such as acetyl acid, propionic acid, and butyric acid (ratio in the colon: 60:25:1543). They are produced in the gastrointestinal tract and enter circulation via the portal vein. SCFAs are important regulators in maintaining an intestinal steady state as well as epithelial cell barrier integrity, and they signal by G-protein coupled receptors (GPCRs) such as GPR41, GPR43, and GPR109A.44 SCFAs not only provide energy to intestinal epithelial cells but also participate in metabolism and in immune and inflammation responses as signaling molecules.

Marques et al.45 discovered that a high-fiber diet can alter the gut microbiome and offer protection against the development of cardiovascular disease. The positive influence of fiber might be due to the SCFA acetyl acid, which is the main metabolite of the gut microbiome. One of the positive effects of acetyl acid results from the transcriptional regulatory factor Egf1, which is the major regulatory factor of cardiovascular disease via fibrosis and inflammation in the heart and kidney, and via cardiomyopathy.45 After experimentation, Zhou et al.46 found that the traditional Chinese medicine Xiao-Qing-Long Tang could exert positive effects by lowering blood pressure and by preventing cardiomyalgia, inflammation, and fibrosis. Xiao-Qing-Long Tang thus efficiently stopped the progress of HFpEF by mitigating intestinal mucosal damage, altering the composition of the gut microbiome, and increasing levels of acetate, propionate, and butyrate.

There have been many studies on the effects of SCFA in protecting cardiac function. We know that SCFAs can help to regulate hosts’ immune systems. For instances, butyric acid can mediate the increase of anti-inflammatory cells such as Tregs, Tr1, and Bregs, and inhibit the increase of pro-inflammatory cells such as macrophages, dendritic cells, neutrophilic granulocytes, and effector T cells.47 SCFAs can also promote restoration after MI by inducing the infiltration of CX3CR1+ monocytes in the area around the MI.48 Meanwhile, SCFAs work to protect the gut barrier.49 For instance, butyric acid promotes the proliferation and differentiation of intestinal epithelial cells, repairs damaged intestinal mucosa and maintains its integrity, and reduces the inflammation caused by external substances such as bacteria and their metabolites entering circulation.50 In addition, SCFAs regulate hosts’ blood pressure.51 Propionic acid induces the release of renin and raises blood pressure by binding with the olfactory receptor Olfr78 expressed by a ring of periglomerular cells.52 However, propionic acid can also induce vasodilation and lower blood pressure by binding with GPR41, a receptor expressed in vessel endothelial cells.52 With these beneficial functions, SCFA might play an important role in preventing the occurrence and development of HF.

**Bile acid (BA)**

BA is an important component of bile. Primary BAs [including cholic acid and chenodeoxycholic acid (CDCA)] are produced in the liver by the oxidation of cholesterol and excreted to the intestinal tract via the biliary system.53 In the intestinal tract, primary BAs are converted to secondary BAs [including deoxycholic acid and lithocholic acid].53 The majority of BA is
reabsorbed in the intestine and reenters the liver via the portal vein, and only a small proportion of BA is eliminated from the body in the feces. The variance of BA can in turn affect the composition of the gut microbiome.54 The physical function of BA is to promote the absorption of dietary fiber, lipid-soluble molecules, and cholesterol.55 Mayerhofer et al.56 conducted a prospective observational single-center study to measure the serum concentration of primary and secondary BA. They discovered that the ratio of primary and secondary BA drops in CHF patients; the main reason for this change was the decrease of primary BA. In addition, though the level of secondary BA remained roughly the same, the composition varied in CHF patients. In single-variant analysis, the ratio decrease was associated with a shorter lifespan.

BA’s receptors include the farnesoid X receptor (FXR) and the G-protein coupled bile acid receptor 1 (TGR5). It has been proven that FXR can alleviate inflammation by inhibiting NF-kB. Given that NF-kB may lead to cardiomegaly, it can be assumed that FXR can improve cardiac function.57 However, Pu et al.58 demonstrated with an in vitro cardiomyocyte experiment that FXR might be the mitochondrial signaling medium of cell apoptosis. This idea was also proved by an experiment in which mice with the FXR gene knocked out showed better restoration after MI due to decreased cell apoptosis and fibrosis.59 Eblimit et al.60 also proved experimentally that TGR5 agonists can induce protective changes in heart cells and improve the response of mouse cardiomyocytes to physical, positive inotropic, and hemodynamic stress.

Interventions based on gut microbiome metabolites

There are many studies proving the close association between the gut microbiome and HF, and how to prevent and treat HF by improving the gut microbiome has become a major focus of research. At present, available interventions include dietary intervention, antibiotic intervention, probiotic and prebiotic treatment, fecal microbiota transplantation (FMT), and TMA-lyase inhibitors.

Dietary intervention

The diversity of the gut microbiome is related to dietary habits, therefore, diet can be changed to alter the structure of the gut microbiome and potentially treat multiple diseases.51 In order to alter the progress of HF, dietary modification focuses on reducing salt intake to prevent hypertension and maintain water-electrolyte balance.73 The American College of Cardiology Foundation and the American Heart Association strongly recommend a plan called Dietary Approaches to Stop Hypertension,61 which involves increasing the intake of fruits, vegetables, grains, and low-fat dairy products, as well as foods such as meat, fish, poultry, nuts, and bean products. Meanwhile intake of sugary foods and beverages, red meat, and added fat is decreased. In a 13-year observational study,62 researchers followed 4478 men and women aged 45–84 who did not have clinical cardiovascular disease at the beginning of the study, surveying them on their dietary intake and evaluating their health. They discovered that the more the participants aged under 75 followed the Dietary Approaches to Stop Hypertension diet, the less likely they were to develop HF. Similarly, a Mediterranean diet was found to prevent and decrease mortality from cardiovascular disease.63 Features of the Mediterranean diet are relatively high intake of grains, vegetables, fruits, nuts, and olive oil, moderate intake of dairy products (mainly cheese and yogurt), fish, poultry, and wine (mainly red wine), combined with relatively low intake of other dairy products, red meat, processed meat, and sugar. In a randomized controlled trial, 980 participants with high cardiovascular risk were given a low-fat or Mediterranean diet. After one year of dietary intervention, it was found that the Mediterranean diet could decrease HF risk factors such as serum N-terminal pro-BNP.64

Probiotic and prebiotic treatment

Probiotics refer to live beneficial microorganisms,77 including Bifidobacteria, yeasts, and Lactobacillus. They can suppress inflammation, protect and restore the intestinal mucosal barrier, and improve intestinal function.65 Prebiotics are defined as selective fermentation products, and they include malt oligosaccharides and oligosaccharides. Prebiotics can benefit hosts’ health by specifically altering the composition and/or activity of the gut microbiome. Gan et al.66 gave rats coronary artery ligation for 6 weeks to induce HF and continuously administered Lactobacillus rhamnosus GR-1, a probiotic, to the rats during this period. They discovered that the probiotic reduced remodeling after coronary artery ligation-induced MI and HF. Vlasov et al.67 induced CHF in rats by injecting phenylephrine subcutaneously for 2 weeks and exercising them. They gave the rats probiotic compounds for 7 days before the start of CHF modeling and throughout the whole study. The result was that endotoxin levels decreased and dysbiosis of the gut microbiome improved in rats receiving probiotic compounds. Recently, a randomized, controlled pilot study with Saccharomyces boulardii was reported to demonstrate that HF patients presented a reduction on biochemical and inflammatory biomarkers, and also improvement on cardiac systolic function, compared with placebo group.83 While probiotic therapy is promising, more research is needed to see if these results are beneficial and substantial in the long term. A similar study involving 150 patients with stable HF, using S. boulardii is under investigation.84

Antibiotic treatment

Many studies have proved the association between gut microbiome dysbiosis and HF, and the most effective and common way to regulate the gut microbiome is with antibiotics. Riba et al.68 studied the influence of doxycycline on cardiomyocyte culture and isoproterenol-induced HF in rats. They discovered that doxycycline improved left ventricular systolic function, thickness of the ventricular wall, and ventricular diameter, and significantly reduced the severity of HF after MI. They proved that doxycycline not only had a protective effect against cardiomegaly, cardiac remodeling, and fibrosis, but also reduced mitochondrial fission and depolarization in cardiomyocytes induced by reactive oxygen species, and effectively regulated the main regulatory factors for mitochondrial fusion and fission: OPA-1, Mfn-2, and Drp-1. Conraads et al.69 proved that the combination of polymyxin B and tobramycin could lower fecal endotoxin levels and levels of cytokines including IL-1β, IL-6, and TNF-α, as well as improving vascular endothelial function. However, levels of these indicators returned to baseline after the antibiotics were stopped. Also, although studies like these show that antibiotics can improve HF, they also kill beneficial bacteria, induce resistance to pathogens, and cause adverse side effects. Therefore, it is important to consider their side effects and clinical efficacy before using them.
Fecal microbiota transplantation

FMT is a medical approach in which gut microbiota from donors is delivered to recipients, altering recipients' gut microbiome composition and enhancing its diversity. FMT is very effective for recurrent and refractory Clostridium difficile infection. In a randomized double-blind controlled trial with 20 metabolic-syndrome patients, researchers found that in patients who received vegetarians' fecal microbiota once, the gut microbiome structure changed but indicators for vessel inflammation did not. At present, there are no studies on FMT in relation to HF, and it is not clear yet whether this approach could improve HF. However, FMT could also transfer viruses from donors to recipients. Therefore, FMT has both positive and negative potential as a treatment approach, and how to make use of the advantages and avoid the disadvantages remains a question worthy of investigation.

Inhibitors of the TMAO metabolic pathway

We already know about the correlation between the TMAO metabolic pathway and poor HF outcome, so we can prevent and treat HF by blocking the TMAO metabolic pathway. A recent study shows that 3,3-dimethyl-1-butanol (DMB) can lower serum TMAO levels. DMB is an analog of choline, and it inhibits microorganisms from producing TMA, thus reducing the production of TMAO. Wang et al. found that by lowering serum TMAO level, DMB negatively regulated the TGF-β1/Smad3 and p38/NF-κB signaling pathways and reduced cardiac remodeling due to pressure overload. Mildronate (Meldonium, a clinical heart-protective medication which lowers L-carnitine levels and decreases TMAO concentration via the THP) is a mechanism-based inhibitor of the TMAO metabolic pathway.

Outlook

The gut, where hundreds of trillions of microorganisms gather, is closely correlated with human health. Studies on gut microbiome metabolites are cautiously emerging, and many of them show that gut microbiome metabolites such as TMAO are likely to become gut microbiota dependent biomarkers for heart failure. Therefore, FMT is a potential treatment approach, and how to make use of the advantages and avoid the disadvantages remains a question worthy of investigation.

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