

Current understanding of gut microbiota alterations and related therapeutic intervention strategies in heart failure

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Abstract

Objective: The purpose of this review is to stress the complicated interactions between the microbiota and the development of heart failure. Moreover, the feasibility of modulating intestinal microbes and metabolites as novel therapeutic strategies is discussed.

Data sources: This study was based on data obtained from PubMed up to March 31, 2019. Articles were selected using the following search terms: “gut microbiota,” “heart failure,” “trimethylamine N-oxide (TMAO),” “short-chain fatty acid (SCFA),” “bile acid,” “uremic toxin,” “treatment,” “diet,” “probiotic,” “prebiotic,” “antibiotic,” and “fecal microbiota transplantation.”

Results: Accumulated evidence has revealed that the composition of the gut microbiota varies obviously in people with heart failure compared to those with healthy status. Altered gut microbial communities contribute to heart failure through bacterial translocation or affecting multiple metabolic pathways, including the trimethylamine/TMAO, SCFA, bile acid, and uremic toxin pathways. Meanwhile, modulation of the gut microbiota through diet, pre/probiotics, fecal transplantation, and microbial enzyme inhibitors has become a potential therapeutic approach for many metabolic disorders. Specifically, a few studies have focused on the cardioprotective effects of probiotics on heart failure.

Conclusions: The composition of the gut microbiota in people with heart failure is different from those with healthy status. A reduction in SCFA-producing bacteria in patients with heart failure might be a notable characteristic for patients with heart failure. Moreover, an increase in the microbial potential to produce TMAO and lipopolysaccharides is prominent. More researches focused on the mechanisms of microbial metabolites and the clinical application of multiple therapeutic interventions is necessarily required.

Keywords: Heart failure; Gut microbiota; Dysbiosis; Treatment

Introduction

Heart failure is the end stage of various cardiovascular diseases (CVDs). The prevalence of heart failure in adults is 1% to 2% and increases to more than 10% in patients over 70 years old.^[1] The lifetime risk of heart failure is 33% for men and 28% for women at 55 years old. Two major components of the pathogenesis of heart failure are pathologic myocardial remodeling and stimulation of the neuroendocrine system, including the renin-angiotensin-aldosterone system and the sympathetic nervous system.^[2,3] The typical symptoms of heart failure include dyspnea, fatigue, and edema of the lower extremities. Some heart failure patients may not exhibit early symptoms, which could lead to missed diagnoses.^[4] According to the onset severity and course of symptoms and signs, heart failure is classified into chronic heart failure and acute heart failure. Heart failure leads to a poor prognosis by negatively affecting the quality of life and impairing

patients' social functioning. Prevention of heart failure, timely diagnosis, and initiation of early treatment are critical to successfully reducing mortality and improving prognosis.

Although physicians have accumulated considerable experience in treating heart failure during the past 30 years, the effectiveness of the current treatment regimen is still far from satisfactory. The high incidence and mortality of heart failure have imposed heavy burdens on medical spending and have become a major public health problem, hindering the economic development of all countries.^[5] The latest European study (previous European Society of Cardiology heart failure study) revealed that the 12-month all-cause mortality rates were 17% for hospitalized patients with heart failure and 7% for outpatients with stable heart failure and that the 12-month readmission rates were 44% and 32%, respectively.^[6] One main reason for the poor prognosis of heart failure is the incomplete

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knowledge we have regarding associated risk factors. Additionally, the available prognostic markers are not sufficiently precise.^[7,8] The gut microbiota plays a critical physiologic and metabolic role in the human body. The gut microbiota could be regarded as an endocrine organ because it not only releases its own products but also metabolizes host metabolites and external nutrients into hormone-like signals, which impact both normal physiologic processes and chronic diseases.^[9] It is not surprising that significant interest is focused on the roles of the human gut microbiota in CVD and metabolic disorders, including heart failure.

Human Gut Microbiota

The human intestine is a large bacterial reservoir containing on its surface over 2000 species and at least 10^{14} bacterial organisms, which is 10 times more than the number of human cells.^[10-12] The entirety of microorganisms that coexist with their hosts refers to the gut microbiota, which contains at least 100 times more genetic information than the human genome.^[11] It is now well established that the human gut microbiome is predominated by phyla such as *Bacteroidetes* and *Firmicutes*. Phyla with lower abundances include *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia*.^[10,13]

The gut microbiota interacts with the host through metabolism-independent pathways such as bacterial translocation-associated endotoxemia and metabolism-dependent pathways, such as the trimethylamine (TMA)/trimethylamine N-oxide (TMAO), short-chain fatty acid (SCFA), bile acid (BA), and uremic toxin pathways.^[9] To some extent, human beings' own cells coexist with the gut microbiota to form a "superorganism." Human genes and the gut microbiota collectively affect metabolism and immune and inflammatory responses.^[14-16]

Physiologic Roles of the Gut Microbiota

In the healthy human gut, the overall microbial community structure remains stable over time within an individual but varies greatly across individuals. Environmental factors that contribute most to interindividual diversity include diet, lifestyle, and antibiotic use. Host genotype, age, and sex also contribute to gut microbiota diversity.^[11,16,17] The gut microbiota can interact with the host and perform multiple physiologic functions. A principal role of the gut microbiota is participating in food digestion and nutrient uptake. The gut microbiota produces SCFAs by breaking down dietary fibers through mainly the saccharolytic pathway.^[13] A major role of SCFAs is serving as energy substrates for epithelial cells of the gut. Binding of SCFAs to G-protein-coupled receptor 41 (Gpr41) can induce expression of the enteroendocrine hormone peptide YY in gut epithelial L cells, which regulates host appetite and helps increase energy harvesting from the diet. The gut microbiota also digests food through the proteolytic pathway, thus contributing to SCFAs production and formation of cometabolites, such as ammonia, various amines, and thiols.^[13] In addition, the gut microbiota plays a role in constituting and regulating intestinal barriers and modulating the host immune system to prevent inappro-

prate inflammation.^[13,18] The gut microbiota assists with the maturation of immunologic tissues by stimulating gut lymphatic tissue, which forms an essential mechanism of defense against pathogens.^[13] Furthermore, the gut microbiota can participate in neurologic development. The "gut-brain axis" refers to the assembly of the gut microbiota and the central, parasympathetic, and sympathetic nervous systems. Altered gut microbial composition is associated with neurodegeneration and neuroimmune activation. Finally, the gut microbiota is also involved in maintaining host energy homeostasis and vitamin synthesis.^[19]

Gut Microbiota and Diseases

Gut dysbiosis refers to quantitative and qualitative alterations in the composition of the gut microbiota, which has been associated with the pathogenesis of a wide spectrum of diseases, including cancer, infectious diseases, inflammatory bowel disease, metabolic diseases such as diabetes and obesity, autoimmune diseases, autism, and CVD.^[20-27] In particular, the relationship between gut dysbiosis and CVD, including hypertension, atherosclerosis, thrombosis and heart failure, has been focused on.^[28-31] Accumulated evidence suggests a potential role that dysbiosis of the gut microbiota might play in the onset and progression of heart failure. An overview of the interactions between gut microbiota and heart failure is seen in Figure 1.

Gut Microbiota Dysbiosis in Heart Failure

The objective of microbiome analysis is to detect and characterize the gut microbiota via assessment and classification of its genomes and corresponding metabolites, therefore finding a more comprehensive explanation for the composition and function of the gut microbiota. With the development of sequencing technology, "16S" analysis, which detects the sequence difference of the hypervariable region of the 16S ribosomal ribonucleic acids for taxonomic identification of bacteria, is able to characterize the gut microbiota at a species-level resolution. Furthermore, metagenomics sequencing, which evaluates the composite genetic material present in the microbiome, is capable of characterizing specific taxa of the gut microbiota at a strain-level resolution. With the help of bioinformatics methods, the current technology enables us to study the underlying relationships between exact compositions of the gut microbiome and CVD.^[11,19,32,33]

For a healthy individual, anaerobic *Bacteroidetes* and *Firmicutes* constitute more than 90% of the total gut bacterial species.^[10] Compared to healthy controls, heart failure patients usually have decreased gut microbial richness and a shift in the composition of the gut microbiota. According to Luedde *et al*'s^[34] research based on 16S rRNA sequencing, a significant decrease in the abundance of Coriobacteriaceae, Erysipelotrichaceae, and Ruminococcaceae at the family level and a significant decrease in the abundance of *Blautia*, *Collinsella*, unclassified Erysipelotrichaceae, and unclassified Ruminococcaceae at the genus level have been shown in the gut of heart failure patients. Moreover, Kummel *et al*^[35]

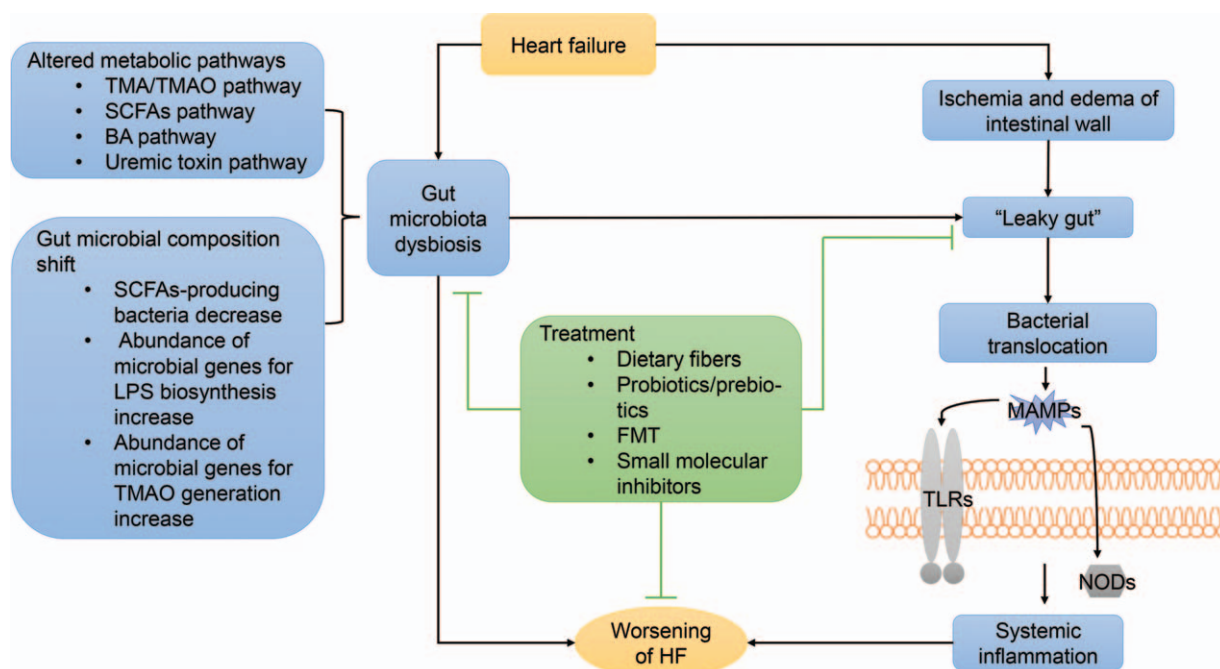


Figure 1: Gut microbiota dysbiosis and bacterial translocation involved in the progression of heart failure. Decreased cardiac output leads to intestinal mucosal ischemia and/or edema, thus leading to a “leaky gut.” Bacterial translocation and systematic inflammation occur subsequently. Moreover, heart failure is accompanied by a shift of the gut microbiota composition as well as varied metabolic pathways, which exacerbate the disease. BA: Bile acid; FMT: Fecal microbiota transplantation; HF: Heart failure LPS: Lipopolysaccharide; MAMPs: Microbe-associated molecular patterns; NOD: Nucleotide oligomerization domain; SCFA: Short-chain fatty acid; TLRs: Toll-like receptors; TMA: Trimethylamine; TMAO: Trimethylamine *N*-oxide.

discovered a depletion of the Lachnospiraceae family, which consists of several butyrate-producing species, in heart failure patients through 16S rRNA sequencing technology. In addition, there is an inverse correlation between Lachnospiraceae and sCD25, which is a T-cell activation marker. Such a correlation was even more prominent in patients whose disease was more severe than in those whose disease was less severe. A 16S analysis based on 22 hospitalized patients with heart failure by Kamo *et al*^[36] also reported a reduction in SCFA-producing bacteria such as *Eubacterium rectale* and *Dorea longicatena*. In addition, a shift in the gut microbiota compositions in different age groups exists. A major butyrate-producing species (*Faecalibacterium prausnitzii*) was revealed to be less abundant in old patients with heart failure than in young patients with heart failure. Metagenomics sequencing technology has also been involved in the identification of the gut microbiome in patients with heart failure. Recently, Cui *et al*^[31] discovered decreased enrichment of *F. prausnitzii*, *Oscillibacter* sp., and *Sutterella wadsworthensis* in fecal samples from heart failure patients through metagenomic analyses. For functional analysis, an elevation in the abundance of microbial genes for lipopolysaccharide (LPS) biosynthesis and TMAO generation and a decrease in microbial genes for butyrate-acetoacetate coenzyme A transferases were noted in the gut microbiota of patients with chronic heart failure. Metabolomic and correlation analyses confirmed that the composition of metabolites in fecal and plasma samples from chronic heart failure patients significantly changed compared with those from healthy controls, and the varied metabolic profile was associated with a shift in the gut microbiome. In addition

to 16S rRNA or metagenomics sequencing, traditional methods for identifying gut microorganisms such as stool sample collection, bacterial incubation, and isolation have been applied to study the gut flora of patients with heart failure. According to Pasini *et al*,^[37] chronic heart failure patients develop an increased abundance of pathogenic bacterial colonies in their stools. Specifically, patients with relatively more severe disease tend to have a significantly increased ratio of *Candida*, *Campylobacter*, and *Shigella* species.

A summary of current research on the composition of gut microbiota in heart failure is shown in Table 1. The summary was based on data obtained from PubMed up to March 31, 2019. Articles were selected using the following search terms: “gut microbiota” and “heart failure.” We reviewed the medical literature one by one.

“Leaky Gut” and Bacterial Translocation in Chronic Heart Failure

Under physiologic conditions, the gut microbiota constitutes an essential part of intestinal mucosal barriers that play a necessary role in systemic immunity and metabolism. Healthy gut microbiota is largely responsible for the overall health of the host. However, under pathologic conditions, the gut microbiota may harm the human body by disturbing normal systemic immunity and metabolism through releasing toxic substances into the peripheral circulation. As early as 1999, scientists hypothesized that the intestinal permeability observed in chronic heart failure patients was altered by edema, which in turn led to bacterial translocation as well as endotoxemia.

Table 1: Current research on the composition of gut microbiota in heart failure by high-throughput sequencing technology.

Author (year)	Patients	Technology	Discovery	References
Luedde <i>et al</i> (2017)	20 patients with HF due to ischemic cardiomyopathy or dilated cardiomyopathy	16S rRNA V1-V2 sequencing	Compared to in control subjects, HF cases showed a significant decrease in Coriobacteriaceae, Erysipelotrichaceae, and Ruminococcaceae at the family level and a significant decrease in <i>Blautia</i> , <i>Collinsella</i> , uncl. <i>Erysipelotrichaceae</i> , and uncl. <i>Ruminococcaceae</i> at the genus level	34
Kummen <i>et al</i> (2018)	44 patients with stable systolic HF	16S rRNA V3-V4 sequencing	Patients with HF had decreased microbial richness; a depletion of the <i>Lachnospiraceae</i> family was remarkable, which consists of several butyrate-producing species; an inverse correlation between <i>Lachnospiraceae</i> and sCD25 was detected.	35
Kamo <i>et al</i> (2018)	22 patients with HF hospitalized for acute decompensated HF or acute exacerbation of chronic HF	16S rRNA V1-V2 sequencing	Abundances of <i>Eubacterium rectale</i> and <i>Dorea longicatena</i> were reduced in HF; <i>Faecalibacterium prausnitzii</i> and <i>Clostridium clostridioforme</i> were less abundant in older patients (≥ 60 years) than they were in younger patients (< 60 years) with HF	36
Cui <i>et al</i> (2018)	29 patients with CHF due to ischemic cardiomyopathy and 24 patients with CHF due to dilated cardiomyopathy	Metagenomic sequencing	A decrease in <i>F. prausnitzii</i> and increase in <i>Ruminococcus gnavus</i> were essential characteristics in CHF; microbial genes for LPS biosynthesis and TMAO generation were up-regulated and genes for butyrate-acetoacetate coenzyme A transferases were down-regulated in CHF	31

HF: Heart failure; uncl.: Unclassified; CHF: Chronic heart failure; LPS: Lipopolysaccharide; TMAO: Trimethylamine N-oxide.

Endotoxemia could trigger systemic inflammatory responses, which aggravate the progression of heart failure.^[38] In 2007, Sandek *et al*^[39] proved that compared with control group subjects, patients with chronic heart failure had increased thickness of the intestinal wall, intestinal permeability, and intestinal insufficiency. Moreover, the serum level of anti-*Escherichia coli* J5 endotoxin IgA was higher in patients with heart failure than that in control subjects. These findings provided evidence for pathologic changes in the gut of patients with heart failure. Based on previous studies, Sandek *et al*^[40] found through in situ fluorescence hybridization that high levels of anaerobic *E. rectale* in the sigmoid colon mucosa (juxtamucosal bacteria) in patients with heart failure were associated with low perfusion of the mucosa. Decreased blood perfusion resulted in exaggerated hypoxia in intestinal villi, which might account for enrichment of gut-specific anaerobes in patients with heart failure. Increased intestinal mucosal bacteria could trigger inflammation in the body by releasing large quantities of endotoxins into the bloodstream, resulting in cachexia.

Currently, the accumulated literature supports the “gut hypothesis of heart failure,” which affirmed the role of the gut in the pathogenesis of heart failure. The gut hypothesis

suggests that decreased cardiac output, aggravating systemic congestion and hypoperfusion, can lead to intestinal mucosal ischemia and/or edema, which creates hypoxia and a hypercapnia status. Subsequently, a decrease in intestinal mucosal pH and diminished passive carrier-mediated transport of D-xylose occurs, leading to a “leaky gut,” which describes increased gut permeability as well as intestinal barrier dysfunction. As a result, increased bacterial translocation occurs, which is accompanied by increased circulating endotoxin release into the peripheral circulatory system. The circulating endotoxins produced by bacteria refer to main structural components of bacteria including LPS, flagellin, peptidoglycans, and formylated peptides, which are recognized as microbe-associated molecular patterns (MAMPs). MAMPs are selectively recognized by pattern recognition receptors (PRRs) such as host Toll-like receptors and nucleotide oligomerization domain-containing receptors. Microbial activation of PRRs could reverse cholesterol transport while promoting insulin resistance and hyperlipidemia.^[9] Furthermore, microbial activation of PRRs either on gut epithelial cells or within the vasculature stimulates the host immune response by triggering numerous downstream signaling processes, thus leading to vascular inflammation.^[15,41] In addition, LPS could activate systemic inflammation by

inducing elevated proinflammatory cytokines such as interleukin-1, interleukin-2, high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor- α , therefore adversely impacting the disease progression of heart failure.^[13,18,19]

Metabolite-Driven Pathways of the Gut Microbiota in Chronic Heart Failure

The gut microbiota can influence host physiologic activities through quantities of processes. In addition to direct translocation of bacteria and releasing gut microbial signals, the gut microbiota can impact hosts through bioactive metabolites that act on distal organs either directly or indirectly.^[42] Accumulated evidence suggests that among the numerous metabolites produced by the gut microbiota, a large portion is biologically active and directly absorbed into systemic circulation, whereas others may serve as mediators between microbes and the host after being further metabolized by host enzymes.^[13,30,43-46] The gut microbiota interacts with the host through a number of pathways, including the TMA/TMAO, SCFA, BA, and uremic toxin pathways.

TMA/TMAO pathway

Novel technologies herald great advances in gut microbiota studies.^[47,48] Wang *et al*^[43] used metabonomics to investigate the relationship between the gut microbiota and CVD. They found that plasma TMA, a metabolite produced by intestinal flora from choline and L-carnitine in food, could be oxidized to TMAO by flavin-containing monooxygenase in the liver. Evidence supports a positive correlation between increased levels of TMAO and the incidence of cardiovascular events in patients with coronary heart disease. Further studies have confirmed that TMAO could promote the process of atherosclerosis.^[44,49] Moreover, scientists have pointed out that TMAO is also associated with heart failure. Tang *et al*^[50] found a positive relationship between plasma TMAO levels and 5-year all-cause mortality in 720 patients with stable heart failure. The TMAO level was higher in patients with heart failure than that in control group subjects. The risk of death increased 3 to 4 times in patients with high plasma TMAO levels compared with patients with low plasma TMAO levels. After adjusting for traditional cardiovascular risk factors and B-type natriuretic peptide (BNP) levels, the increased TMAO level still predicted an increased 5-year mortality rate. Suzuki *et al*^[51] also examined plasma TMAO levels in 972 patients with acute heart failure and evaluated the relationship between TMAO levels and in-hospital mortality, all-cause mortality, and the overall incidence of death or readmission due to heart failure within a year. Elevated TMAO levels were correlated with unfavorable outcomes in patients with acute heart failure. In addition, the combination of TMAO levels and N-terminal pro-BNP (NT-proBNP) values could more precisely predict the mortality risk of hospitalized patients with acute heart failure than TMAO levels alone.

Furthermore, Tang *et al*^[52] confirmed that the plasma TMAO levels in patients with chronic heart failure were higher than those in healthy controls. In addition, in patients with heart failure, increased levels of TMAO were

associated with relatively poor New York Heart Association (NYHA) grades. Patients with high TMAO levels had worse left ventricular diastolic dysfunction and clinical prognoses than patients with low TMAO levels. In a prospective observational study (155 patients with heart failure, 100 patients with stable coronary heart disease, and 33 healthy controls were included), plasma TMAO levels in patients with heart failure were significantly higher than those in the controls. In addition, TMAO levels were positively associated with increases in NYHA grade and NT-proBNP levels. TMAO levels were not related to the levels of LPS or left ventricular ejection fraction (LVEF), but they were negatively correlated with the non-transplant history of chronic heart failure patients.^[53]

Another study in 2016 showed increased incidences of pulmonary edema, higher atrial natriuretic peptide levels, and enhanced left ventricular remodeling, and aortic arch constriction in mice fed with choline or TMAO than those in control mice. A diminished ejection fraction observed in the treated mice also indicated an exacerbation of heart failure.^[54] It has been reported that plasma choline, betaine, and TMAO levels are correlated with BNP levels and electrocardiogram indices of diastolic function but not systolic function. TMAO levels were associated with poor prognosis in chronic systolic heart failure after adjustment for cardiorenal indices.^[55] The known pathways of TMAO formation and its relationship with heart failure are present in Figure 2.

SCFA pathway

SCFAs are major products of microbial fermentation of dietary fibers in the gut. Both the saccharolytic pathway and proteolytic pathway participate in the production of SCFAs, but the former contributes more than the latter. Since several correlation analyses have revealed a remarkable decrease of SCFA-producing bacteria in patients with heart failure, a cardioprotective role of SCFAs seems to exist. SCFAs seem to promote post-infarction cardiac repair through inducing infiltration of CX3CR1+ monocytes in the peri-infarct zone.^[56] Accumulated evidence indicates that SCFAs play a role in mediating the host immune system. For example, butyrate plays an anti-inflammatory role through inducing Foxp3+ Treg cell proliferation and suppressing the generation of Th17 cells by activating G protein-coupled receptor 43.^[57] Moreover, SCFAs play a gut barrier-protective role. Through activating the hypoxia-inducible factor, butyrates help to maintain the physiologic relative hypoxia state in colon epithelial mucosa, which is essential in maintaining gut barrier function.^[58] In addition, SCFAs could modulate host blood pressure. Propionate, which is an SCFA shown to induce vasodilation *in vitro*, could modulate mouse blood pressure in a mutually antagonistic way. Propionate induces renin secretion and thus elevates blood pressure through binding to Olfr78, which is an olfactory receptor expressed in the renal juxtaglomerular apparatus. However, propionate also presents powerful hypotensive effects by binding to Gpr41, which is another SCFA receptor expressed in smooth muscle cells of small vessels.^[59] Considering the roles that SCFAs play in gut barrier protection, blood pressure modulation, and the immune system, SCFAs probably play an essential role in

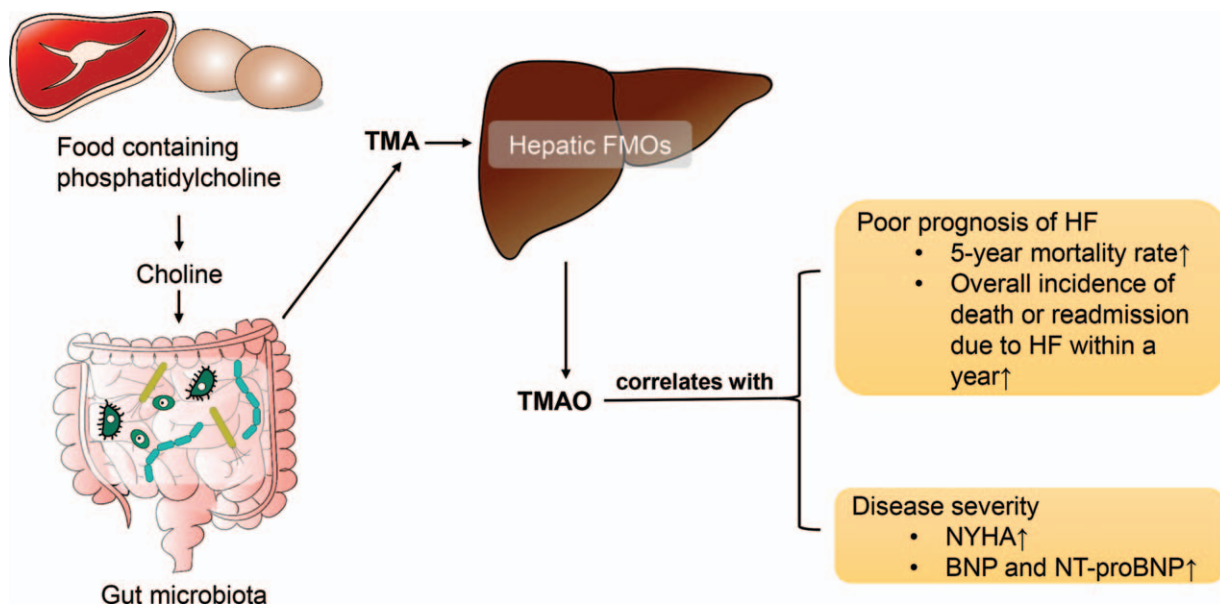


Figure 2: Pathways of trimethylamine *N*-oxide formation and its relationship with heart failure. TMA is formed through metabolism of choline and choline-containing compounds from diets by gut microbiota in the intestinal lumen. TMA can be absorbed from the intestine and delivered to the liver where FMO convert it to TMAO. It is found that TMAO is correlated with poor prognosis and severity of HF. BNP: B-type natriuretic peptide; FMO: Flavin-containing monooxygenase; HF: Heart failure; NT-proBNP: N-terminal pro-BNP; NYHA: New York Heart Association; TMA: Trimethylamine; TMAO: Trimethylamine *N*-oxide.

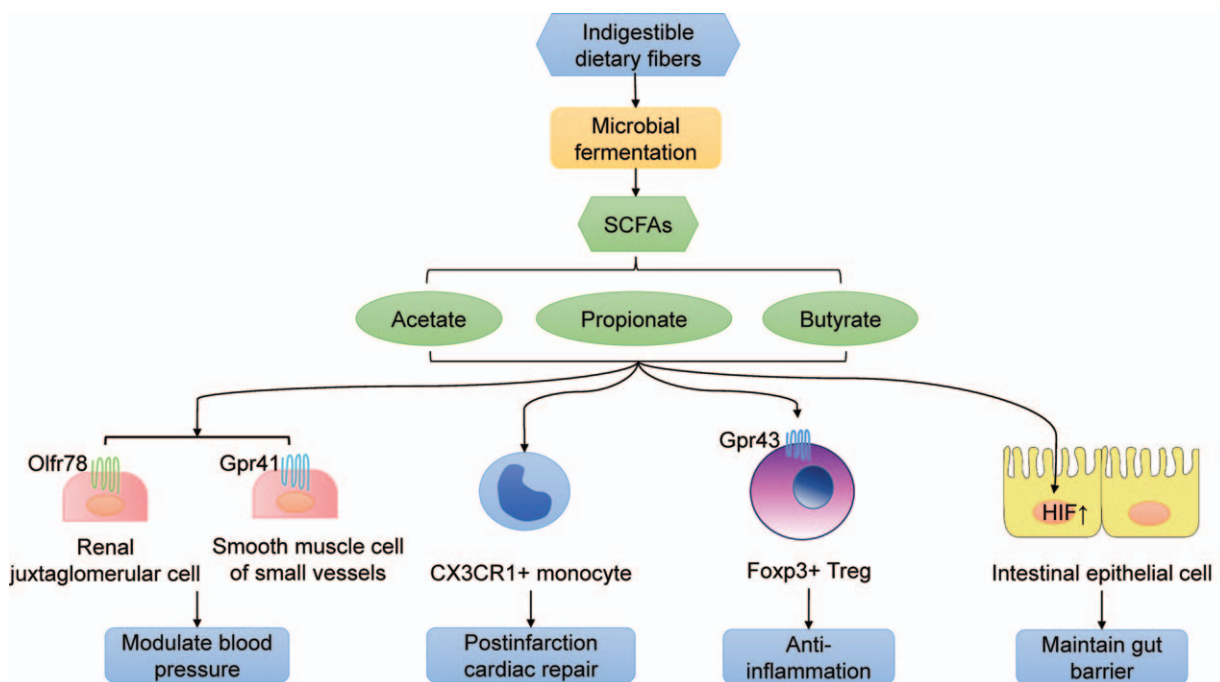


Figure 3: Roles of short-chain fatty acids involved in cardiovascular diseases. SCFAs are major products of microbial fermentation of dietary fibers. SCFAs mainly present cardioprotective effects, including modulating blood pressure, promoting post-infarction cardiac repair, anti-inflammation and maintaining gut barrier. Gpr41: G-protein-coupled receptor 41; Gpr43: G-protein-coupled receptor 43; HIF: Hypoxia-inducible factor; SCFA: Short-chain fatty acid; Treg: Regulatory T cell.

pathways associated with heart failure, which still requires further investigation. A summary of the known cardio-protective roles of SCFAs is present in Figure 3.

Bile acid pathway

Primary BAs are produced in the liver and secreted into the gut through the biliary system. It is well established that the

gut microbiota profoundly impacts BA metabolism by promoting deconjugation, dehydrogenation, and dihydroxylation of primary BAs.^[60] The physiologic function of BAs is to facilitate the absorption of dietary fat, fat-soluble molecules and cholesterol.^[61] Farnesoid X receptor is highly expressed in the liver and ileum, which negatively regulates BA synthesis by regulating distinct transcriptional networks. However, tauro-beta-muricholic acid

(T β MCA), which is an abundant primary BA, could up-regulate the BA pool size and composition by acting as a farnesoid X receptor antagonist. It is suggested that particular microbiota may have the capacity to suppress BA synthesis by reducing the levels of T β MCA.^[60] According to a cross-sectional study, an increased ratio of secondary to primary BAs in serum was found in patients with chronic heart failure, and this ratio was revealed to be associated with reduced overall survival in univariate analysis.^[55] Considering that the production of secondary BAs depends on the gut microbiota, identifying specific BAs and correlated microbial enzymes as well as host receptors might help for understanding the underlying mechanism through which the gut microbiota plays a role in modifying BA composition and thus impact metabolic disorders involved in the progression of heart failure.

Uremic toxin pathway

It is well accepted that CVD and chronic kidney disease are closely interrelated via the so-called cardiorenal syndrome, which could accelerate the progression of failure in both organs.^[18] The microbial urease of the gut microbiota is able to hydrolyze urea to form ammonia, which is later transformed into ammonium hydroxide, leading to the production of uremic toxins such as indoxyl sulfate and *p*-cresyl sulfate. It was reported that indoxyl sulfate and *p*-cresyl sulfate were associated with adverse cardiovascular outcomes. A direct effect of indoxyl sulfate on cardiomyocytes is the stimulation of cardiac fibroblasts and collagen synthesis via activation of the p38 mitogen-activated protein kinase, p42/44 mitogen-activated protein kinase, and nuclear factor κ B pathways, thus leading to adverse cardiac remodeling.^[17,62]

Targeting the Gut Microbiota for Treatment

The already known correlations between altered gut microbial compositions and susceptibility for cardiometabolic disorders remind us of the possibility of the gut microbiome as a potential novel target for therapeutics. Regulating the gut microbiota has shown promising prospects in curing various diseases, including diabetes, cancer, and so on.^[63-65] Three major intervention principles have been focused on, namely, targeting microbiota compositions, targeting metabolic pathways, and applying mucosal barrier protectors. We discuss mainly treatment strategies based on modulating gut microbiota compositions and metabolic pathways in this review.

A summary of current research on targeting gut microbiota for the treatment of heart failure is shown in Table 2. The summary was based on data obtained from PubMed up to March 31, 2019. Articles were selected using the following search terms: “gut microbiota,” “heart failure,” “cardiovascular disease,” “treatment,” “diet,” “probiotic,” “prebiotic,” “antibiotic,” and “fecal microbiota transplantation.” We reviewed the medical literature one by one.

Diet modulation

Currently, diet modulation represents a major therapeutic strategy utilized to treat chronic metabolic diseases in

clinical practice.^[66] Many clinical studies proved that dietary nutritional intervention was effective in reducing cardiovascular risk.^[67-70] A retrospective cohort study based on 3215 post-menopausal female participants revealed that relatively high dietary approaches to stop hypertension diet scores were modestly associated with a low mortality in women with heart failure. The Mediterranean diet presented a trend toward an association with decreased heart failure mortality, although statistical significance was not reached.^[71] It has been reported that a high-fiber diet can prevent the development of heart failure and effectively improve myocardial remodeling in hypertensive mice by increasing the abundance of acetate-producing microbiota.^[69] However, although many studies confirmed that dietary interaction was associated with improved cardiac function and heart failure biomarkers, few of them focused on the impact that such lifestyle intervention had on the gut microbial community structure and function as well as the underlying mechanistic interplay.^[72,73] Studies exploring the impact of dietary interventions on heart failure from the perspective of the gut microbiome in humans are needed.

Probiotics/prebiotics

Probiotics are defined as live “beneficial” bacteria utilized to re-establish an appropriate intestinal balance. Potential mechanisms of probiotics include mainly pH modulation, antibacterial substance production, and competition with pathogens.^[74,75] Plasma cytokine levels are generally increased in patients with heart failure, and inflammatory pathways are widely involved in the onset and development of chronic heart failure.^[76] Regulating the intestinal microecosystem may be a potential therapeutic strategy to improve cardiac function and clinical prognosis by optimizing gut flora metabolism and reducing inflammation responses in humans. Another approach to achieve similar effects on modulating intestinal microbiota is the use of prebiotics. Prebiotics are defined as “selectively fermented ingredients that result in specific changes, in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health.”^[77] Typical prebiotics refer to indigestible molecules such as oligosaccharides or complex saccharides. According to Gan *et al*'s^[78] research, although no changes in the gut microbial compositions were detected by 16S rRNA sequencing afterwards, oral supplement of *Lactobacillus rhamnosus* GR-1 can effectively attenuate left ventricular hypertrophy and significantly improve hemodynamic parameters in post-infarction heart failure rat models. This effect may be achieved by improving myocardial metabolite status, such as decreasing the leptin/adiponectin plasma concentration ratio. In another animal experiment, Lin *et al*'^[79] reported that probiotic-fermented purple sweet potato yogurt might reverse congestive heart failure induced by hypertension through attenuating cardiomyocyte apoptosis by inhibiting Fas receptor-dependent apoptotic pathways but activating compensatory IGF-IR-dependent pathways in spontaneously hypertensive rats. Similar findings were validated in humans, as Costanza *et al*'^[80] conducted a randomized placebo-controlled pilot trial focusing on

Table 2: Current research on targeting gut microbiota for the treatment of heart failure.

Treatment	Author (year)	Research objects	Intervention	Research method	Conclusions	References
Diet	Levitan <i>et al</i> (2013)	3215 post-menopausal female patients hospitalized for HF	None	Retrospective cohort study	Higher DASH diet scores were associated with lower mortality in women with HF; a trend toward an association between higher Mediterranean diet scores and lower mortality in women with HF existed but did not reach statistical significance.	79
	Marques <i>et al</i> (2017)	C57BL/6 mice underwent sham or DOCA surgery	Oral uptake of high-fiber diet or acetate	Animal experiments and 16S sequencing	Acetate-producing bacteria increased in the gut microbiota; supplementation of fiber and acetate lowered blood pressure, decreased cardiac hypertrophy and fibrosis, and improved heart function in experimental HTN	77
Probiotics	Lin <i>et al</i> (2013)	Spontaneously hypertensive rats	Oral uptake of <i>Lactobacillus acidophilus</i> -fermented purple sweet potato yogurt	Animal experiments	Cardiomyocyte apoptosis was attenuated by inhibiting the Fas receptor-dependent apoptotic pathway and activating the compensatory IGF-IR-dependent survival signaling pathway	86
	Gan <i>et al</i> (2014)	Male Sprague-Dawley rats underwent coronary artery ligation surgery	Oral uptake of <i>Lactobacillus rhamnosus</i> GR-1	Animal experiments and 16S sequencing	Attenuated left ventricular hypertrophy and improved cardiac function; improved myocardial metabolite status; no change in the gut microbial composition was detected compared to that of controls	85
	Costanza <i>et al</i> (2014)	20 NYHA class II or III HF patients with an LVEF <50%	Oral uptake of <i>Saccharomyces boulardii</i>	A randomized, double-blind, placebo-controlled pilot trial	Patients with chronic systolic HF submitted to a short-term probiotic therapy presented an improvement in LVEF ($P = 0.005$) and a reduction in left atrial diameter	87

(continued)

Table 2
(continued).

Treatment	Author (year)	Research objects	Intervention	Research method	Conclusions	References
	Tang <i>et al</i> (2019)	C57BL/6J mice underwent LAD ligation surgery	Oral supplementation of <i>Lactobacillus</i> probiotic	Animal experiments and 16S sequencing	Supplementation of <i>Lactobacillus</i> probiotic increase survival rate of post-infarction mice pre-treated with antibiotics; Probiotic supplementation increase the level of myeloid cells in the hearts of mice	59
Antibiotics	Conraads <i>et al</i> (2003)	10 patients with CHF (NYHA classes III–IV)	Oral uptake of enteral a non-absorbable polymyxin B/tobramycin regimen	Non-randomized, non-placebo-controlled pilot study	Antibiotics eradicated intestinal aerobic gram-negative bacilli and reduced fecal endotoxin concentrations; a significant decline in inflammatory biomarkers and improved vascular endothelial function were discovered	91
	Lam <i>et al</i> (2012)	Dahl S rats underwent ischemia/reperfusion surgery	Oral uptake of vancomycin	Animal experiments and microbial DNA qPCR	Vancomycin led to altered abundance of microbial species and reduced total microbe number; cardioprotective effects including smaller infarct size, decreased circulating leptin levels and improved recovery of post-ischemic mechanical function were discovered	89

HF: Heart failure; DASH: Dietary approaches to stop hypertension; DOCA: Deoxycorticosterone acetate; HTN: Hypertension; IGF-IR: Insulin-like growth factor-I receptor; NYHA: New York Heart Association (classification); LVEF: Left ventricular ejection fraction; LAD: Left anterior descending coronary artery; CHF: Chronic heart failure.

treating chronic systolic heart failure patients with *Saccharomyces boulardii* probiotics, which yielded a decrease in cholesterol, uric acid, and left ventricle diameter; an improvement in LVEF; and a reduction in left atrial diameter.

Antibiotics

Scientists tried to cure disease by eliminating the pathogens. It has been reported that oral administration of vancomycin significantly impacts host microbiota diversity by inducing a decrease in gram-positive bacteria and a compensatory increase in gram-negative bacteria. Subsequently, BA dihydroxylation and peripheral insulin sensitivity were suppressed as a result.^[81] Lam *et al*^[82,83] suggested that taking vancomycin orally led to a reduced total microbial number in Dahl S rats and presented cardioprotective effects including reduced

myocardial infarction size and reduced circulating leptin levels in an ischemia/reperfusion rat model. According to Conraads *et al*,^[84] selective decontamination of the digestive tract (SDD, using an enteral non-absorbable polymyxin B/tobramycin regimen) induced decreased fecal endotoxin concentrations and showed anti-inflammatory effects. In addition, improved vascular endothelial function presented as an increase in flow-mediated dilation. However, the listed variations returned to baseline levels after discontinuation of the SDD. Although antibiotics show cardiovascular protective impacts to some extent, such impacts seem to be limited within the period of medication. In addition, antibiotics usually reduce the total microbiota in the gut, which probably includes beneficial bacteria. Currently, the general consensus for antibiotic intervention is that such non-specific antimicrobial approaches may be more harmful than beneficial.

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) aims at introducing fecal contents from healthy subjects into the gut of patients, which seems to be effective in the treatment of recurrent or refractory *Clostridium difficile* infection (CDI).^[85] However, for most diseases except CDI, the efficacy of FMT is somehow limited according to current studies.^[86] In addition, the potential risk of transferring endotoxins or infectious agents may cause adverse complications.^[13] Further studies will be required to optimize factors such as dosing, delivery route, and formulation of FMT to improve the therapeutic efficacy. It is also anticipated that whole-microbiome transplantation will eventually be replaced by transplantation of a defined group of bacteria.^[86]

Molecular inhibitors of the TMAO pathway

Recent studies have revealed clear links between the TMAO pathway and poor prognosis of heart failure. The development of a small molecule drug for inhibiting microbial generation of TMA has become a potential therapeutic strategy for CVDs.^[29] The 3,3-dimethyl-1-butanol, a choline structural analog, is able to inhibit microbial generation of TMA from quantities of nutrients. Although temporarily there is no evidence supporting that a TMA/TMAO inhibitor can improve heart failure, this molecular therapy has shown great potential in treating heart failure. This potential also reminds us of the possibility of developing other molecular drugs as research on gut microbiomes and metabolomics progresses in the field of heart failure.

Conclusions and Perspectives

Currently, heart failure remains a major health burden. The rapid development of high-throughput sequencing technology enables us to uncover the previously unappreciated complexity of the gut microbiome. Since Wang and Tang *et al*'s impressive research thoroughly revealed the interplay between gut microbes and atherosclerosis through the TMA/TMAO pathway, it has gradually become consensus that the gut microbiota contributes to cardiovascular pathophysiology via multiple metabolic and physiologic pathways. Through the identification of bacterial metabolites, it is possible for us to explore numerous microbial pathways that may be involved in the pathogenesis of cardiometabolic disorders and search for potential biomarkers for diagnosis and treatment. Except for the many clinical studies that have already demonstrated an association between TMA/TMAO and adverse outcomes of patients, a few studies based on 16S or metagenomics sequencing have discovered a reduction in SCFA-producing bacterial species in patients with heart failure, especially some butyrate-producing species such as *F. prausnitzii* and *E. rectale*. In addition to being major energy substrates of gut epithelial cells, SCFAs play essential roles in the maintenance of host glucose homeostasis and the immune system. A shift in the gut microbiota into a composition lacking in SCFA-producing bacteria might be a notable characteristic for patients with heart failure. Future studies are needed to explore the deep

correlations between microbes, SCFAs and host cardiovascular health.

By modulation of gut microbiota composition and function through diet, pre/probiotics, FMT, and microbial enzyme inhibitors, it may become feasible for us to alter metabolic profiles in a preferred direction that is beneficial for host health in the long term. Transplantation of a defined group of bacteria or utilization of special microbial enzyme inhibitors, such as DMB, can probably adjust blood levels of biologically active microbial-derived metabolites by modulating gut microbial compositions or targeting specific microbial pathways, thus achieving a more personalized and accurate therapeutic intervention. However, neither approach has been studied to date in patients with heart failure. Future research is required to complement this gap. Finally, the use of pre/probiotics has shown great potential in treating heart failure. However, most studies have focused on a correlation between the oral uptake of probiotics and changes in heart failure phenotypes; only a few studies have explored the variations of gut microbial compositions and functions brought about by intervention with pre/probiotics, let alone the underlying metabolic and physiologic mechanisms. Pre/probiotics remain a cost-effective and practical option for intervention that is an area of active investigation, but mechanistic understanding is strongly needed.

Although several studies revealed significant correlations between either the gut microbiota composition or their derived metabolites and the phenotypes of heart failure, the sample size of each study is not large enough. Heart failure is the end stage of cardiogenic diseases and is usually accompanied by multiple complications. Many factors including etiology, complications, drugs, host genetic heterogeneity, and lifestyles may contribute to confounding effects in the clinical study. Therefore, well-designed, prospective, and longitudinal clinical studies based on large cohorts are still needed to reveal the actual transformation of the gut microbiota composition and metabolic profile in heart failure.

Doubtlessly, a striking and intriguing association exists between the gut microbiota and the cardiovascular system that probably plays a large role in CVDs. However, few studies have investigated in depth a direct role of the gut microbiota in heart failure and associated complications at the mechanistic and causal levels. Further investigations are definitely in demand to better understand intermicrobial interactions and microbial-host interactions and how they are related to the underlying molecular entities involved in disease progression.

Cardiac disease has been a burden throughout history. With improved quality of life and prolonged life expectancy, the prevalence of cardiac diseases currently continues to escalate, which means that more people will enter the stage of heart failure. More innovative diagnostic and therapeutic approaches for heart failure are urgently in demand. As we gradually gain a deeper understanding of gut microbiota and heart failure interplay, the question of how to bring microbial information into clinical practice remains a major challenge. Of course, high-throughput

technologies including 16S and metagenomics sequencing can provide profound information about a single patient's gut microbiota compositions, but such technologies are quite expensive and no evidence clearly clarified their utility in clinical practice as yet. Instead, studying metabolic profiles in blood and urine may be a practical way to guide personalized interventions. Undoubtedly, further investigations to explore the translational potential of mechanism research and the clinical application values of multiple therapeutic interventions are necessarily required.

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Conflicts of interest

None.

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