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BIOMARKERS OF HEART FAILURE (W TANG & J GRODIN, SECTION EDITORS)

Gut Microbiome and Precision Nutrition in Heart Failure: Hype or Hope?

Thanat Chaikijurajai [1,2] · W. H. Wilson Tang [1,3]

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Abstract

Purpose of Review Over the past decade, the gut microbiome has been shown to play an important role in the pathogenesis of heart failure (HF) and serves as a mediator that links host genomes and environmental exposure (especially dietary intake) to the development and progression of HF. Given that alterations in gut microbial composition and metabolism are commonly seen in patients with HF, the use of gut microbial metabolites as diagnostic and prognostic biomarkers, as well as novel therapeutic targets for HF, is promising.

Recent findings Alterations in gut microbial composition and function have bidirectional relationships with HF. Gut microbial metabolites, including short-chain fatty acids, bile acids, trimethylamine *N*-oxide (TMAO), and amino acid metabolites, have been shown to play a significant role in HF. For example, TMAO has been consistently demonstrated as an independent predictor of worse prognosis in patients with HF, and a potential therapeutic target for cardiac remodeling and HF. However, clinical studies on dietary interventions targeting gut microbial metabolites have demonstrated inconsistent findings, which could be from variations in the study population, gut microbial communities, and study designs.

Summary Measurement of gut microbial metabolites can improve risk stratification and potentially identify HF patients who are more likely to respond to personalized pharmacologic or dietary interventions targeting specific pathways associated with the gut microbiome.

Keywords Gut microbiome · Heart failure · Short-chain fatty acid · Bile acids · TMAO

Introduction

Heart failure (HF) has been one of the leading causes of morbidity and mortality, which accounts for 6.2 million patients, and over 1 million hospitalizations per year in the USA [1]. Although recent advances in treatment modalities have been shown to significantly reduce the risk of death and HF hospitalization, the mortality and rehospitalization rates remain unacceptably high regardless of left ventricular ejection fraction (EF) [2]. Therefore, novel insight into pathogenesis and pathophysiology of HF can lead to the development of more precise risk stratification and personalized comprehensive therapeutic approaches.

Over the past decade, the gut microbiome has been implicated to play an important role in the development and progression of HF and its comorbidities [3, 4]. Gut microbes filter and metabolize dietary nutrients and produce a variety of metabolites that can act as signaling molecules. Therefore, the gut microbiome can be considered a major endocrine organ directly influenced by dietary intake, which may have a greater influence on cardiometabolic profile compared to dietary macronutrients [5•]. In addition, dietary molecules can also affect gut microbial function and metabolism by modulating their gene expression [6]. Since each person's dietary habit and gut microbial composition and function are different, targeting the gut microbiome may be an important key to personalized lifestyle or dietary modification, therapeutic interventions, and development of precision HF medicine.

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✉ W. H. Wilson Tang
tangw@ccf.org

[1] Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk J3-4, Cleveland, OH 44195, USA

[2] Department of Internal Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[3] Center for Microbiome and Human Health, Department of Cardiovascular and Metabolic Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

Accumulating evidence suggests that changes in composition and metabolism of gut microbial communities contribute to a worse prognosis of both acute and chronic HF. Despite recent advances in microbial gene sequencing, the validity and reproducibility of the techniques used for identifying gut microbes are still evolving [7]. Instead, researchers have recently focused on the metabolomic approach for studying the gut microbial function and the complex relationship between host and microbes in HF. In this review, we discuss the interaction between HF and intestinal structure and function, gut microbial dysbiosis in HF, and gut microbiome-mediated metabolism and metabolites that have been shown to be associated with HF.

Gut Hypothesis in Heart Failure

The concept of how the gastrointestinal system is mechanistically linked to the pathogenesis of HF (often referred to as the "gut hypothesis of HF") has been described since the early 2000s [8]. Hemodynamic features of HF can directly affect intestinal mucosa structure and function in different ways. Elevated intracardiac filling pressure and systemic venous congestion can cause bowel wall edema, whereas decreased cardiac output, adaptive redistribution of systemic perfusion, and venous hypertension may result in intestinal hypoperfusion and ischemia [3, 8]. It is believed that both bowel wall congestion and splanchnic ischemia may contribute to the disruption of intestinal mucosal barrier, increased intestinal permeability, and subsequent translocation of the gut microbiome and its components. Specifically, bacterial endotoxin and metabolites may enter into the systemic circulation, thereby activating immune response and inflammation [8–10], which is a major contributor to the development and progression of HF [11, 12]. Furthermore, endotoxin and inflammatory cytokines can also promote intestinal permeability [13–16], resulting in a vicious cycle of gut microbial endotoxin translocation, systemic inflammation, and worsening HF.

Besides inflammation, bowel wall ischemia, edema, and translocation of bacterial endotoxin can also worsen HF through different mechanisms. For instance, intestinal hypoxia and acidosis upregulate sodium-hydrogen exchanger 3 (NHE3) expression on intestinal epithelial cells, resulting in increased sodium and water absorption, and subsequent HF decompensation [17]. In addition, lipopolysaccharide (LPS), a virulence factor and endotoxin of Gram-negative bacilli, is able to bind to toll-like receptor 4 (TLR-4) on cardiomyocytes, resulting in decreased ventricular contractility [18–20]. Interestingly, LPS was found to be elevated in patients with decompensated HF and could be attenuated by diuretic drugs [21] and antibiotic therapy [22]. In chronic HF patients, LPS and inflammatory biomarkers track with the severity of HF [23]. However, advanced HF therapy (left ventricular assist device and heart transplantation) can reduce inflammation but not endotoxemia [23]. Interestingly, Jennings et al. [24] also demonstrated that gut microbial composition, endotoxemia, and inflammation were associated with the required dose of tacrolimus in heart transplant patients. Therefore, it is conceivable that the gut microbiome plays an important role in every stage of HF, from cardiac injury to end-stage HF and even after transplantation.

Meanwhile, the intense interaction between cardiovascular and gastrointestinal systems in HF exists and involves gut microbiome, immune response, and fluid balance [3]. In the future, indirect assessment of bowel wall integrity by measuring gut microbial endotoxin may lead to better risk prediction of HF decompensation, and novel therapeutic approaches targeting intestinal barrier function.

Patterns of Gut Dysbiosis in Heart Failure

Recently, a variety of patterns of changes in human gut microbial composition have been shown to be associated with HF [3]. For instance, the incidence of *Clostridium difficile* infection, which can occur following the disruption of commensal gut bacteria by antibiotics, was higher in patients with HF [25]. These observations support the hypothesis that HF might be associated with the overall depletion of the gut microbiome [23, 26, 27, 28••], as well as an increase in the abundance of some pathogenic Gram-negative bacteria [29]. In addition, some genera of the gut microbiome have also been shown to be enriched in HF, such as *Ruminococcus gnavus* [30•], *Bacteroidetes*, *Prevotella*, *Hungatella*, and *Succiclasticum* [28]. Even though research has focused on the association between altered gut microbial composition and HF, there have been a lot of discrepancies in the findings, which could be a result of diverse gut microbial communities, as well as significant variations in the structure and function of gut microbes [31]. Therefore, given the large amount of data and variable findings, we may have to rely on artificial intelligence and machine learning to better integrate the data in order for clinicians to gain more insight into the interpretation and utility of gut microbial genome and taxonomic profiling in HF patients [32].

Gut Microbiome-Derived Metabolites as Biomarkers in Heart Failure

Throughout life, the gut microbiome serves as an intestinal filter of a variety of dietary nutrients and produces metabolites, which are then reabsorbed into the bloodstream, and act as signaling molecules either with or without biochemical modification by host enzymes. Indeed, some of the

metabolites have been shown to play a significant role in the host's susceptibility to HF and are associated with adverse outcomes over time. Also, it is believed that interpersonal variation in the composition and function of the gut microbiome, as a result of different genomes and environmental exposure, may contribute to different severity and prognosis among HF patients, independently of traditional risk factors [3, 33]. Interestingly, disrupted circadian rhythm was also shown to negatively impact the function of the gut microbiome, leading to impaired ischemic cardiac healing and subsequent HF [34]. Nevertheless, identifying the composition and abundance of gut microbes requires complicated and sophisticated stool sample processing, including 16S rRNA gene sequencing and whole metagenomic shotgun sequencing. However, stool samples are often more challenging to collect, and analytical techniques are clinically less available and reproducible, in contrast to quantifying their circulating metabolites using metabolomic approaches [35, 36]. Hence, the use of gut microbial metabolites is relatively more pragmatic. However, while some previous clinical studies have demonstrated potential effects of different dietary interventions on gut microbial metabolites, their findings have been inconsistent (Table 1) [37–74], which could be explained by the diverse study population, different study designs, and variations in gut microbial composition and function.

Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are produced by gut microbes from the fermentation of indigestible nutrients, such as dietary fiber, complex carbohydrates, resistant starch, and prebiotics, which serve as a major energy source and protectors of intestinal mucosa [75]. As a result, the altered metabolism of SCFAs is associated with disruption of the intestinal barrier and dysbiosis of the gut microbiome [76, 77]. Furthermore, SCFAs can also be absorbed into the enterohepatic and systemic circulation. Animal studies have demonstrated that SCFAs can bind to specific G protein-coupled receptors, thereby regulating blood pressure and renin-angiotensin-aldosterone system (RAAS) [78]. Interestingly, acetate can also be protective against mineralocorticoid-induced cardiac hypertrophy and fibrosis by the downregulation of cardiac and renal early growth response (*Egr1*), a transcription factor that regulates inflammation, ventricular hypertrophy, and cardiorenal fibrosis [79••]. Despite accumulating evidence suggests that HF patients have a significantly lower abundance of SCFA-producing gut microbes as assessed by 16S ribosomal RNA sequencing in fecal samples [30, 80, 81•], the use of plasma SCFA levels remains to be elucidated with only preliminary data from Sarah et al. [82] showing that HF patients had decreased plasma propionate and butyrate levels compared to healthy individuals. However, there are discrepancies on the role of a high-fiber diet and SCFA supplementation as potential therapeutic interventions in HF. Marques et al. [79••] showed that mice fed with a high-fiber diet and acetate had improved gut microbial profile, as well as attenuated blood pressure, inflammation, cardiac hypertrophy, and cardiorenal fibrosis. Similarly, a study on 84 patients with systolic HF revealed that low fiber intake was associated with gut microbiome dysbiosis, which led to a significantly higher risk of mortality and heart transplantation [28]. In contrast, in a mouse model of genetic dilated cardiomyopathy, fiber and acetate supplementation were not able to protect cardiomyocytes from apoptosis or adverse remodeling [83]. Therefore, the benefits of a high-fiber diet and SCFAs in patients with HF, especially those with lower SCFA levels or SCFA-producing microbes, are still under active investigations.

Bile Acids

Primary bile acids are emulsifiers produced by the liver from cholesterol, which facilitate the digestion and absorption of dietary fats and fat-soluble vitamins in the small intestine before being reabsorbed via enterohepatic circulation. Unabsorbed primary bile acids will then enter the colon in which the gut microbiome converts primary into secondary bile acids using bile salt hydrolases [84]. Interestingly, evidence has shown that bile acids are able to cause both favorable and unfavorable effects on cardiac structure and function. For instance, early studies showed that primary bile acids

Table 1 Effects of dietary interventions on gut microbial metabolites from clinical studies

Dietary intervention	SCFAs	Bile acids	TMAO	Amino acid metabolites
Probiotics	↑/→ [37–41]	↑/↓/→ [42–45]	↑/→ [46–48]	↑/↓ [49–52]
Fermented dairy product	N/A	↓/→ [53, 54]	↓ [55]	N/A
Mediterranean diet	↑/→ [56–59]	N/A	→ [60–62]	→ [60]
Vegetarian diet	↓ [59]	↓ [63, 64]	↓ [65, 66]	↓ [67, 68]
Caloric restriction	↑ [69]	↑/↓ [70–72]	↓ [73]	N/A
Intermittent fasting	N/A	N/A	↓ [74]	N/A

N/A, not applicable; *SCFAs*, short-chain fatty acids; *TMAO*, trimethylamine *N*-oxide

caused negative inotropic and chronotropic effects on cardiac muscle in rats [85, 86]. In addition, bile acids can also promote cardiac apoptosis and fibrosis following ischemic injury by binding to the farnesoid X receptor [87, 88]. In contrast, it is also believed that bile acids suppress nuclear factor-κB [89], a transcription factor that regulates inflammation and mediates cardiac hypertrophy and remodeling [90]. Moreover, activation of another type of bile acid receptors, Takeda G protein-coupled receptor 5 (TGR5), improves myocardial survival and response to stress [91].

Similarly, clinical studies also showed conflicting results on the type of bile acids associated with favorable outcomes in HF patients. For example, Mayerhofer et al. [92] demonstrated that HF patients had significantly higher ratios of secondary to primary bile acids, which were also associated with adverse clinical outcomes. On the other hand, HF patients supplemented with ursodeoxycholic acid, a secondary bile acid, had improved peripheral blood flow and lower inflammation [93]. Hence, it is possible that imbalance of bile acids, either an increase or decrease, is associated with the development and progression of HF, and the optimal values of both primary and secondary bile acids need to be determined, in order to utilize bile acids as prognostic biomarkers and therapeutic targets in HF.

Trimethylamine *N*-Oxide

Among previously discovered gut microbiome-mediated metabolites, trimethylamine *N*-oxide (TMAO) has been the most widely investigated gut microbiome-related biomarker in the cardiovascular field. TMAO is produced by gut microbes from choline, phosphatidylcholine, and L-carnitine, which can be found in eggs, red meat, dairy products, and some deep-sea fish [36, 94, 95]. It is now recognized that the enterohepatic circulation recycles choline and other nutrients thru biliary secretion, rendering a constant supply to the colonic microbes (and not just thru oral ingestion). Initially, choline and phosphatidylcholine are converted directly into trimethylamine (TMA) by gut microbial enzymes, TMA lyases, whereas L-carnitine (primarily from red meat sources) needs to be converted into γ-butyrobetaine, which is then metabolized by TMA lyase to form TMA [96]. Subsequently, TMA in the intestinal lumen is absorbed into the circulation and converted into TMAO by host enzymes, predominantly hepatic flavin monooxygenase 3 (FMO3) [97]. Not only has TMAO been mechanistically linked to atherosclerosis [96–98] but it has also been shown to play an important role in the pathogenesis of HF, including increased maladaptive ventricular remodeling [99], cardiac mitochondrial dysfunction [100], and impaired calcium regulation [101]. Interestingly, Li et al. [102] demonstrated that TMAO causes cardiac fibrosis and hypertrophy through transforming growth factor-β1 (TGF-β1)/Smad3 signaling activation, which are the same pathways observed in TMAO-mediated renal fibrosis [103]. Nevertheless, the exact mechanisms or cellular receptors by which TMAO promotes HF still remain to be elucidated.

Recent research has shed light on the role of TMAO as a diagnostic and prognostic biomarker in both acute and chronic HF. In chronic HF with reduced EF (HFrEF) patients, TMAO levels are significantly elevated and associated with HF severity and poor prognosis [104–108], albeit not tracking with titration of guideline-directed medical therapy [109••]. Interestingly, in heart transplant patients, an increase in γ-butyrobetaine is associated with acute graft rejection and atherosclerotic burden [110]. Similarly, elevated baseline TMAO has been shown to be an independent predictor of mortality and rehospitalization in patients with acute decompensated HF [111, 112]. However, studies on TMAO levels in patients with HF with preserved EF (HFpEF) have shown conflicting findings. Schuett et al. [113•] showed that TMAO was not associated with mortality in 395 patients with HFpEF, whereas TMAO was shown to be a good predictor for both short-term and long-term mortality and hospitalization in 118 patients with HFpEF [114]. Therefore, these findings support the complexity of the pathophysiology and phenotypes of HFpEF, and further investigations on the role of TMAO in HFpEF are needed.

In addition to being a novel biomarker in HF, TMAO has also been shown to be a potential therapeutic target in HF. Organ et al. [115••] showed that iodomethylcholine, a nonlethal microbial TMA lyase inhibitor that directly targets TMA production, improved cardiac function and prevented cardiac remodeling in a mouse HF model receiving a high choline diet. Similarly, Wang et al. [116••] demonstrated that 3,3-dimethyl-1-butamol (DMB), another nonlethal TMA lyase inhibitor, could attenuate pressure overload-induced cardiac hypertrophy and fibrosis by modulating TGF-β1/Smad3 signaling pathways. Given that the Mediterranean diet contains natural DMB found in extra-virgin olive oil [117], this finding may explain how the Mediterranean diet reduces the risk of incident HF as shown in some studies [118–120], whereas contradicting results were also shown [121, 122]. Similarly, there are also discrepancies in the effects of probiotics on TMAO levels. Even though Matsumoto et al. [123] demonstrated that *Bifidobacterium animalis* subsp. *lactis* LKM512 supplementation reduced TMA production in healthy subjects, other studies failed to show a significant impact of probiotics on TMAO levels [46–48].

These conflicting findings have led to the hypothesis that a reduction in the risk of developing HF following a Mediterranean (or non-red meat) diet may only be seen in patients who have significantly elevated baseline TMAO levels, which needs to be confirmed by post hoc analyses on previous studies, or clinical trials enrolling patients with elevated TMAO. Hence, since there are significant inter-

individual variations in TMAO production and metabolism, TMAO measurement may identify patients who are more likely to benefit from therapeutic and dietary interventions targeting TMAO and subsequently lead to personalized treatment strategies and dietary recommendation, which serves as a fundamental of future precision HF medicine.

Amino Acid Metabolites

In addition to previously mentioned dietary nutrients, some specific amino acids, including tryptophan, tyrosine, and phenylalanine, can also be fermented and metabolized to uremic toxins by gut microbes, especially in patients with impaired kidney function [124]. Often considered as "uremic toxins," the gut microbiome metabolizes tryptophan into indole, which is then converted into either indole-3-propionate (IPA) or indoxyl sulfate (IS). IPA has been shown to counteract the gut hypothesis of HF by protecting the intestinal mucosal barrier, reducing inflammation and gut dysbiosis [125, 126]. This hypothesis is supported by a clinical study demonstrating that patients with dilated cardiomyopathy had significantly less IPA levels [127]. In contrast, IS promotes maladaptive cardiac remodeling and fibrosis by activating inflammation and renin receptors [128–131]. Shimazu et al. [132] revealed that elevated IS was associated with diastolic dysfunction and adverse outcomes. Similarly, tyrosine and phenylalanine are converted into *p*-cresyl sulfate (PCS), which can activate RAAS, and cause cardiomyocyte apoptosis [131, 133]. Moreover, it also disrupts gap junctions and calcium regulation of cardiomyocytes [134]. Interestingly, compared to IS, PCS was shown to be a better independent predictor of mortality and hospitalization in HF patients [135]. Hence, the role of these uremic toxins in the development and progression of HF may become more important in patients with the cardiorenal syndrome, which could potentially lead to specific dietary restrictions or therapeutic interventions in this group of patients. For instance, Asanuma et al. [136] showed that a reduction in IS levels by a uremic toxin absorbent (AST-120) attenuated myocardial fibrosis and apoptosis in a dog model of right ventricular pacing-induced HF. These findings may imply that gut microbial metabolites such as IS can serve as potential mechanism biomarkers.

Conclusion and Future Direction

Altered hemodynamic status in HF affects the composition and function of the gut microbial community, whereas certain strains of gut microbes exert functional consequences (potentially via their metabolites) that can directly or indirectly contribute to the development and progression of HF. Gut microbial metabolites, including SCFAs, bile acids, TMAO, and amino acid metabolites, represent the complex host-microbe relationship. Genomic sequencing of the gut microbiome to date has been unable to confer clear diagnostic or prognostic information, and there is much hype on probiotic therapies that replace or diversify microbial species in the setting of dysbiosis. However, there is much hope that measuring microbial metabolites that are stable in biospecimens (e.g., TMAO, IS) may have the potential to facilitate better risk stratification in patients with HF and may identify subgroups of patients who are more likely to benefit from specific pharmacologic or dietary interventions. Since inter-individual variations in gut microbiome caused by different genomes and environmental exposure exist, gut microbial metabolites may help identify novel endophenotypes of HF by uncovering their underlying pathophysiologic underpinnings. For example, a subset of patients with the accumulation of "uremic toxins" despite relatively preserved renal function as measured by serum creatinine may signify an evolving chronic cardiorenal syndrome. Further studies will require the availability and standardizing of assay techniques, combined with the novel (and more specific) therapeutic strategies to target abnormalities identified by these mechanism biomarkers in order to change the clinical course of disease progression.

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Declarations

Conflict of Interest Dr. Chaikijurajai has no relationships to disclose. Dr. Tang is a consultant for Sequana Medical A.G., Owkin Inc, and Relypsa Inc, and has received an honorarium from Springer Nature for authorship/editorship and American Board of Internal Medicine for exam writing committee participation, all unrelated to the contents of this paper.

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