HHS Public Access

Author manuscript

Curr Heart Fail Rep. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Curr Heart Fail Rep. 2016 April ; 13(2): 103–109. doi:10.1007/s11897-016-0285-9.

Exploring the Microbiome in Heart Failure

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Abstract

Recent years have brought interesting insights into the human gut microbiota and have highlighted its increasingly recognized impact on cardiovascular (CV) diseases, including heart failure (HF). Changes in composition of gut microbiota, called dysbiosis, can trigger systemic inflammation, which is known to be involved in the pathophysiology of HF. Trimethylamine N-oxide (TMAO), which is derived from gut microbiota metabolites of specific dietary nutrients, has emerged as a key contributor to cardiovascular disease pathogenesis. Elevated TMAO levels have been reported to be associated with poor outcomes in patients with both HF and chronic kidney disease (CKD). Dysbiosis of gut microbiota can contribute to higher levels of TMAO and the generation of uremic toxins, progressing to both HF and CKD. Therefore, this bidirectional relationship between HF and CKD through gut microbiota may be a novel therapeutic target for the cardiorenal syndrome. However, the mechanisms by which gut microbiota could influence the development of heart failure are still unknown, and there are still some questions regarding the causative effects of TMAO and the underlying mechanistic link that explains how TMAO might directly or indirectly promote CV diseases including HF. Further studies are warranted to clarify the function of TMAO on the pathophysiology of cardiorenal syndrome and the handling of TMAO levels by the kidneys.

Keywords

Heart failure; Gut microbiota; Cardiovascular disease; Trimethylamine N-oxide; Chronic kidney disease; Cardiorenal syndrome

Introduction

Heart failure (HF) is a growing health problem and a major cause of mortality and morbidity in the world. The pathophysiological concept of HF has changed dramatically during the last

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Conflict of Interest

Takeshi Kitai declares that he has no conflict of interest.

Jennifer Kirsop and W.H. Wilson Tang have received grants from the National Institutes of Health during the conduct of the study.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

decade with an increased understanding of the heart as an endocrine organ, leading to a multiorgan neurohormonal response and an activation of systemic inflammation. However, an even better understanding of the pathophysiology of HF is needed to develop more specific and effective therapies.

Gut microbiota play critical physiological roles in the extraction of energy from our food and in the control of local or systemic immunity. However, in addition to these beneficial functions for the host they can also have negative pathophysiological interactions with the host. For example, gut microbiota and microbiome compositions appear to be involved in the pathogenesis of diverse diseases such as obesity, diabetes, gastrointestinal diseases, cancer and cardiovascular (CV) diseases, including HF.[1–9]

Trimethylamine N-oxide (TMAO), which is derived from gut microbiota produced metabolites of specific dietary nutrients, has emerged as a key contributor to CV disease pathogenesis.[3, 4, 6, 7, 10] Changes in composition of gut microbiota, called dysbiosis, can contribute to higher levels of TMAO and the generation of uremic toxins, progressing to both HF and renal impairment. Currently, antibiotics, prebiotics, probiotics and symbiotics are the instruments utilized in clinical practice to modulate the intestinal microbiota both in healthy and pathologic conditions. These have achieved promising preliminary results in prevention and therapy for obesity and related metabolic diseases.[2, 11] This review will focus on recent progress in our understanding of the interaction of gut microbiota and HF, with a particular emphasis on the cardiorenal syndrome.

The role of the intestinal microbiota

The human intestine harbors a large and complex community of microbial cells that constitute the gut microbiota. The whole microbial genome of the gut microbiota is called the gut microbiome, which is 100 times greater than the human genome.[12] Beyond its role in supporting physiological functions in host digestion, gut microbiota performs a multitude of other functions and interactions with the host. For example, gut microbiota regulates the development and function of mucosal barriers, controls nutrient uptake and metabolism, assists with maturation of immunological tissues and prevents propagation of pathogenic microorganisms.[13]

Gut microbiota participates in food digestion through two main catabolic pathways that can be categorized as saccharolytic or proteolytic. In the saccharolytic pathway, the gut microbiota is responsible for production of short-chain fatty acids, which are known to exert a protective action and a positive immune-modulating activity,[14] guaranteeing a general healthy status. The second catabolic pathway is represented by protein fermentation, which also induces short-chain fatty acid formation and leads to other co-metabolites such as ammonia, amines, thiols, phenols and indoles, some of which are potentially toxic and are considered microbial uremic toxins. Collectively, the microbiota exerts a fundamental influence on systemic immunity and metabolism. A healthy gut microbiota is largely responsible for the overall health of the host.[15]

Gut barrier function and intestinal immunity

The intestinal epithelium is a single layer of cells that are responsible for maintaining a mucosal barrier between the host and the intestinal contents, which is incredibly important in protecting the host from infection and inflammation. This physical barrier is created through the secretion of mucous and water, as well as tight junction proteins at the apical junctions between cells.[16, 17] Epithelial cells produce mucus to shield the epithelium and immune system from direct contact with the microbiota,[18] and the microbiota can prevent the development of inappropriate inflammation, which in turn allows the microbiota to survive in the absence of unnecessary inflammation. Thus, communication between the intestinal microbiota and the host epithelial immune system helps to control the level of mucosal inflammation.

Several recent studies have suggested that disruption of the mucosal barrier function and subsequent gut microbiota-derived endotoxemia could contribute to the pathogenesis of cardiometabolic diseases.[19–22] Disruption of the mucosal barrier in genetically modified or high fat diet-induced obese mice increased local production of lipopolysaccharides by gram-negative bacteria residing in the gut lumen, resulting in a reduced expression of tight junction proteins in the intestinal epithelial cells and increased gut permeability.[23] This permits leakage of lipopolysaccharides into the circulation, which can trigger systemic inflammation and the generation of cytokines like tumor necrosis factor alpha (TNFα) and interleukin 6 (IL-6).[24, 25] Importantly, low-grade leakage of lipopolysaccharides has been seen in patients with obesity, diabetes and HF, potentially contributing to systemic inflammation. [19, 20]

Another possible mechanism of increased permeability of the intestinal wall is hypoxia. The intestine is a blood-demanding organ, and reduced cardiac output and/or intestinal edema due to systemic congestion in HF puts patients at high risk of nonocclusive intestinal ischemia.[26] The presence of intestinal ischemia has been shown in chronic heart failure patients by surrogate markers such as a decrease in intestinal mucosal pH[27] or diminished passive carrier-mediated transport of D-xylose.[28] Importantly, in advanced HF with cardiac cachexia, the intestinal morphology, permeability and function of the intestine are substantially altered.[28–30]

Intestinal dysbiosis in the pathogenesis of systemic inflammation

Composition of the gut microbiota is not constant but differs between individuals and can fluctuate markedly within an individual. In the healthy gut, anaerobic Bacteroidetes and Firmicutes contribute more than 90% of the total bacterial species.[31] However, the ratio of the Firmicutes:Bacteroidetes is not the same in all individuals. Interindividual variation in bacterial diversity is caused by differences in both host genomes and environmental factors, such as antibiotic use, lifestyle, hygiene and diet. An altered gut microbial composition, known as dysbiosis, may be unfavorable and may predispose an individual to disease. Developments in genome sequencing technologies and bioinformatics have now enabled scientists to study these intestinal microorganisms, their functions and microbe-host interactions in an intricate manner in both healthy and diseased hosts.

Recent studies have shown that changes in gut microbiota composition differ and may be related to the pathogenesis of metabolic diseases like obesity and diabetes. For example, patients with type 2 diabetes mellitus had lower proportions of butyrate-producing Clostridiales species and greater proportions of non-butyrate-producing Clostridiales, suggesting a protective role of butyrate-producing bacteria against diabetes.[22] In another study, obese patients were shown to have an increased ratio of Firmicutes to Bacteroidetes in comparison with lean individuals, and this ratio shifted in response to weight loss.[21] Moreover, the composition of intestinal microbiota can shift rapidly during intestinal ischemia and reperfusion[32] or an increase in portal vein pressure.[33] Taken together, these data suggest that the composition of gut microbiota may be altered in HF patients.

Gut microbiota in the pathogenesis of heart failure

Immunological and inflammatory processes probably play an important role in the pathogenesis and progression of HF.[34] Proinflammatory cytokines, such as TNF-α, IL-1, IL-2, IL-6 and C-reactive protein (CRP), are all elevated in patients with HF.[35, 36]

Elevated levels of TNF-α and IL-6 are correlated with the severity of cardiac dysfunction and prognosis.[37] As cited above, intestinal wall edema in HF patients due to systemic congestion and reduced intestinal blood flow may increase bacterial translocation into the circulation, endotoxin absorption and cytokine production.[26–30] Cytokine production and activation can, in turn, provoke inflammation, fibrosis and microvascular and myocardial dysfunction. Niebauer et al. found that HF patients with peripheral edema had higher plasma concentrations of endotoxin and inflammatory cytokines compared to those without edema. After short-term diuretic treatment, serum concentrations of endotoxin, but not cytokines, fell.[38] In another study, HF patients with lower intestinal blood flow were shown to have higher serum concentrations of immunoglobulin A–antilipopolysaccharide, which in turn was correlated with increased growth of bacteria obtained from biopsies of colonic mucosa but not stool bacteria. The nature of the bacterial flora in these subjects also appeared to be different from that in the control subjects.[39]

TMAO as a marker of cardiovascular impairment

In addition to the bacterial components that can induce inflammation, certain bacterial metabolites can also exert cytotoxicity and promote inflammation. One such metabolite is trimethylamine (TMA), an organic compound that is generated by the gut microbiota from dietary phosphatidylcholine, choline and carnitine. TMA is rapidly oxidized into TMAO by flavin monooxygenase enzymes in the liver, and then released into the circulation. TMAO is mainly cleared from circulation by the kidneys, and thus renal function is also important to consider when looking at levels of TMAO in the systemic circulation.[3, 10, 40]

Several studies have suggested that elevated concentrations of plasma TMAO is a new risk factor for CV disease.[3, 4, 10, 41] In a study including more than 4,000 participants undergoing elective coronary angiography, elevated fasting plasma TMAO levels were shown to predict major adverse cardiac events over a 3-year period, independent of traditional CV risks factors, inflammatory markers and renal function.[4] In a more recent clinical study, plasma TMAO levels were increased in patients with HF compared to levels

found in healthy controls. These higher plasma TMAO levels were associated with a 3.4-fold increase in mortality risk, independent of cardiorenal indexes.[5] Further, elevated TMAO levels accounted for the observed increase in CV disease risk associated with elevated plasma concentrations of choline or betaine (another TMA precursor).[41] These data support a strong link between TMAO and CV pathology. However, although plasma levels of TMAO correlate with CV risk, there are still some questions regarding the causative effects of TMAO and the underlying mechanistic link that explains how TMAO might directly or indirectly promote CV disease. For example, the mechanism explaining why patients with HF have increased levels of TMAO remains to be determined. Further studies are warranted to determine whether changes in TMAO directly affect CV disease risk or vice versa.

Intestinal dysbiosis and the cardiorenal syndrome

Cardiovascular and kidney diseases are closely interrelated, and the so-called cardiorenal syndrome (CRS) is associated with poor clinical outcomes.[42] A bidirectional heart–kidney interaction in CRS usually leads to accelerated progression of failure in both organs.[42] In the CKD population, HF is the most common clinical presentation of CV disease. However, traditional CV risk factors are insufficient to explain the extraordinarily high prevalence of CV disease in the CKD population, and potential mechanisms that promote disease progression of cardio-renal syndrome are largely unknown.

Microbiota and the production and intestinal adsorption of uremic toxins

It is well known that the composition of gut microbiota is markedly altered in CKD patients,[43, 44] leading to an influx of circulating urea and other uremic toxins into the gut lumen.[45] Within the intestinal tract, urea is hydrolyzed by microbial urease to form large quantities of ammonia, which is then converted to ammonium hydroxide. Ammonia and ammonium hydroxide disrupt the intestinal epithelial tight junctions.[44] This is thought to be a major cause of intestinal epithelial barrier dysfunction in CKD that allows the translocation of gut bacterial DNA and uremic toxins into systemic circulation, resulting in systemic inflammation.[46–48] Recently, gut microbiota has been detected in the plasma of CKD patients on chronic hemodialysis using 16s rDNA amplification technique, and the presence of gut microbiota in these patients was correlated with increased plasma inflammatory markers such as C-reactive protein and interleukin-6.[49] Non-dialyzable protein-bound uremic toxins such as indoxyl sulfate and p-cresyl sulfate have been investigated as promotors of pathogenesis of CRS. Both of these sulfates are derived from gut microbiotic metabolism of dietary amino acids and are ineffectively cleared from the circulation in cases of renal dysfunction.[50] These gut-derived uremic toxins may contribute to the accelerated progression of both CKD and HF.[50] Further, these uremic toxins are independent predictors of elevated CV risk.[51] This vicious feedback circle of gut dysbiosis, heart disease and kidney disease plays an important role in the development of CRS.[52, 53] Therefore the gut could be a target of treatment of CRS in conjunction with efforts to improve dialysis techniques to better remove these uremic toxins.

Renal handling of TMAO

Trimethylamine N-oxide levels have been found to be high among CKD patients with or without HF, and higher TMAO levels were associated with higher mortality and progressive loss of kidney function.[5–7, 54] As previously mentioned, the concentration of TMAO in blood plasma varies by several factors, including the amount of dietary choline and carnitine ingested, gut microbiota composition and activity, and the activity of host flavin monooxygenase enzymes. It has been found that a dietary choline challenge increases the concentration of TMAO, whereas treatment with broad-spectrum antibiotics reduces TMAO concentration in the blood.[3] Alterations in gut permeability or the dysbiosis of gut microbiota offer potential pathways for higher CV risk in these populations.[55, 56] However, decreased renal clearance of TMAO may also confound this association, as TMAO is predominately excreted in urine.[3, 54]Increased plasma and urine TMAO levels may also be a consequence of the release of TMAO from the renal medulla following ischemic kidney damage,[57] because TMAO may serve as an osmotic agent in the kidney medulla to produce concentrated urine and protect kidney cell proteins from perturbations caused by urea.[58] The role of TMAO as an osmolyte in other human organs has not yet been well investigated.

To date, there are few published reports on TMAO metabolism in patients with CKD.[6, 59] However, given that TMAO clearance is largely dependent on renal excretion,[60] it is not surprising that TMAO levels are elevated in patients with CKD. Indeed, we reported elevated TMAO concentrations in the CKD patient population with associated accelerated atherosclerosis in this population.[6] However, there was only modest correlation between TMAO levels and either estimated glomerular filtration ratio (eGFR) ($r=-0.48$) or cystatin C ($r=0.46$).[6] Recently, Stubbs et al. examined the relationship between circulating TMAO concentrations and eGFR in patients with CKD.[61] In this study, serum TMAO levels demonstrated an inverse association with eGFR and were reduced significantly following renal transplantation. They also found a modest correlation between TMAO levels and eGFR ($r^2=-0.31$).[61] These data suggest that renal handling of TMAO is not a simple process and that an as yet unknown function of TMAO as an osmolyte may contribute to this process. It is clear that further studies exploring the physiology of TMAO generation and metabolism are warranted to more thoroughly define the etiology of TMAO elevations in both HF and CKD.

Modulation of intestinal dysbiosis as a therapeutic target in Heart Failure

As gut dysbiosis has been shown to contribute to the pathogenesis of both HF and CKD, it could be an effective therapeutic target for HF with or without cardiorenal compromise. Diet modification, prebiotics and probiotics are the major therapeutic tools utilized in current clinical practice to modulate gut dysbiosis, but there are few data regarding the impact of these interventions on HF patients.

Dietary intervention

It has been reported that gut dysbiosis, as shown by altered patterns of enterotype dominance, is subject to modification by dietary and environmental variables.[62, 63] Even

a short-term diet of five days can modify the microbiota community, promoting a relative shift of microbiota population abundance in response to either a plant-based or an animal-based diet.[64] Moreover, Almoosawi et al. found that a high level of variability in microbiota significantly correlated with dietary habits, confirming the shaping effect of long-term dietary patterns on gut microbiota.[65] Indeed, the Mediterranean diet is a modern nutritional recommendation originally inspired by the traditional dietary patterns of Greece, Southern Italy and Spain. It is based on a considerable consumption of carbohydrates, primarily unrefined grains, high quantities of fruits, vegetables, legumes, nuts, olive oil and fish and a moderate consumption of red wine. Importantly, the consumption of dairy products and red meats is low.[66] It is well assessed in published literature that adherence to the Mediterranean Diet leads to a decrease in all-cause mortality and in the incidence of CV diseases.[67] Whether or not the Mediterranean diet can modulate TMAO levels and attenuate CV risks in the setting of heart failure remains to be determined.

Application of probiotics and prebiotics

Probiotics are live beneficial bacteria administered to re-establish an appropriate intestinal balance. Probiotics act through different mechanisms including pH modulation, antibacterial compound production and competition with pathogens.[68] Simenhoff et al. reported that administration of lactobacillus, a commonly used probiotic, correlated with a significant reduction of toxins produced by the small intestine, such as dimethylamine and nitrosodimethylamine, in patients with CKD on chronic hemodialysis.[69] In a pilot study, improvements in both symptoms and quality of life were found in CKD patients who received 6 months of supplementation with probiotics.[70]

Another strategy for modulating intestinal microbiota is the use of prebiotics, which are food indigestible molecules such as oligosaccharides or complex saccharides. Prebiotics are used as fermentation substrates and stimulate the proliferation and activity of beneficial intestinal bacteria. Prebiotics have proven effective in improving both glycemic control and plasma lipid profiles.[71] For example, three months of oligofructose supplementation in obese patients was associated with weight loss and improved glucose tolerance.[11] Moreover, modulation of the gut dysbiosis with antibiotics or prebiotics improved gut permeability, reduced metabolic endotoxemia, lowered inflammation and alleviated glucose intolerance in patients with diabetes.[72] Further large interventional studies, as well as a better understanding of gut microbial composition and its functions, are needed to confirm these promising preliminary results in HF patients.

Conclusion and Future Perspective

The gut microbiota plays an important role in overall health, and an imbalance in the composition of the gut microbiota can contribute to an increase in chronic systemic inflammation and the generation of uremic toxins. Both of these consequences have been linked to the pathophysiology of heart failure, particularly in the setting of cardiorenal compromise. However, the specific mechanisms through which gut microbiota influence the development of heart failure are still unknown.

Recent research on TMAO offers new insights into the intestine-heart-kidney interaction and the pathophysiology of heart failure and the cardiorenal syndrome. Further studies are unquestionably warranted to identify the specific gut microbiota responsible for elevated TMAO levels, and long-term intervention studies are needed to clarify the benefits of modulating TMAO as well as using it as a CV risk marker.

Acknowledgments

Dr. Tang is supported by research grants from the National Institutes of Health (R01HL103931, P20HL113452, R01DK106000).

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