Reviews in Endocrine and Metabolic Disorders (2019) 20:407–414
https://doi.org/10.1007/s11154-019-09519-7

The gut microbiome and heart failure: A better gut for a better heart

Maxime Branchereau[1] · Rémy Burcelin[1] · Christophe Heymes[1,2]

Published online: 9 November 2019

Abstract
Despite the development of new drugs and therapeutic strategies, mortality and morbidity related to heart failure (HF) remains high. It is also the leading cause of global mortality. Several concepts have been proposed to explore the underlying pathogenesis of HF, but there is still a strong need for more specific and complementary therapeutic options. In recent years, accumulating evidence has demonstrated that changes in the composition of gut microbiota, referred to as dysbiosis, might play a pivotal role in the development of several diseases, including HF. HF-associated decreased cardiac output, resulting in bowell wall oedema and intestine ischaemia, can alter gut structure, peamibility and function. These changes would favour bacterial translocation, exacerbating HF pathogenesis at least partly through activation of systemic inflammation. Although our knowledge of the precise molecular mechanisms by which gut dysbiosis influance HF is still limited, a growing body of evidence has recently demonstrated the impact of a series of gut microbiome-derived metabolites, such as trimetylamine N-oxide, short-chain fatty acids or secondary bile acids, which have been shown to play critical roles in cardiac health and disease. This review will summarize the role of gut microbiota and its metabolites in the pathogenesis of HF. Current and future preventive and therapeutic strategies to prevent HF by an adequate modulation of the microbiome and its derived metabolites are also discussed.

Keywords Gut microbiota · Dysbiosis · Heart failure · Microbiota-derived metabolites · Treatment

1 Introduction

Heart failure (HF) is the clinical manifestation and the last common process of many forms of cardiovascular disease. Despite the recent development of new drugs and therapeutic strategies, mortality and morbidity related to HF remains high. It is also the leading cause of global mortality. The prognosis after first admission to hospital is poor, with a mortality rate of more than 50% over 5 years. The poor prognosis of patients is partly due to the fact that the disease is not only a hemodynamic disorder, but also a multisystem disorder including a deregulation of many endocrine systems and also uncontrolled inflammatory responses. Due to this high mortality, reflecting at least in part the possibility that important pathogenic mechanisms are not targeted by the current therapeutic options, other factors such as gut microbiota dysbiosis have also been implicated as major risk factors for the development of cardiovascular diseases, including HF [1–3].

Gut microbiota homeostasis is essential for maintaining human health in many aspects, digesting host indigestible nutrients, producing vitamins and hormones, shaping the development of the mucosal immune system, and preventing pathogenic bacteria colonization [4–7]. There is growing evidence that imbalances in the composition and function of gut microbiome, known as dysbiosis, may play an important and independent role both in the prognosis and the development of HF. Tang et al. were the first to develop the "gut hypothesis of heart failure." The gut hypothesis implies that decreased cardiac output in HF can lead to a decrease in intestinal perfusion, muscosal ischemia, leading to a disrupted intestinal mucosa. These changes in intestinal barrier function in turn can lead to increased gut permeability, gut dysbiosis, bacterial translocation and increased circulating endotoxins that can contribute to the underlying inflammation associated with HF [8–10]. However, research supporting this hypothesis so far is mainly of an associative nature. In recent years, beyond the primordial role of bacteria, the challenge was to move from previous associative studies to those that elucidate the cause-effect relationship between gut microbiome dysbiosis and HF. Recent

✉ Christophe Heymes
christophe.heymes@inserm.fr

[1] Institut des Maladies Métaboliques et Cardiovasculaires, INSERM U1048, Université de Toulouse, UPS, Toulouse, France

[2] INSERM U1048 - Institute of Cardiovascular and Metabolic Diseases - I2MC, 1 avenue Jean Poulhès - BP 84225, 31432 Toulouse Cedex 4, France

studies have demonstrated that the gut microbiome can also have an impact on host processes and diseases development via bioactive metabolites, which could be absorbed into the systemic circulation.

In this review, we will discuss how gut microbiome and microbiota-derived metabolites may contribute to the pathophysiology of HF, and evaluate how gut interventions can lead to novel therapeutic targets for HF.

2 Gut microbiota and heart failure

2.1 Alterations in gut microbial composition in HF

As in virtually all cardiovascular diseases, changes in intestinal microbial composition have been described in several cohorts of HF patients. Sandek and colleagues were the first to demonstrate bacterial overgrowth and increased bacterial adhesion in sigmoid mucosa from HF patients [11, 12]. These first results have been confirmed by Pasini and colleagues, who have demonstrated that HF patients are characterized by an intestinal proliferation of pathogenic microorganisms, such as *Candida*, *Campylobacter*, *Shigella*, and *Yersinia*. The authors also demonstrated that the proliferation of these pathogenic bacteria were associated with thickened large bowel walls, increased intestinal inflammation and permeability, and clinical disease severity [13]. More recently, Luedde et al. were the first to realize, using high-throughput sequencing of bacterial 16S rRNA gene sequences, the systematic analysis of intestinal microbiota in HF patients [14]. Unlike early studies using traditional culture techniques on stool samples, the authors could not detect any significant increase in the abundance of specific and potentially pathogenic bacteria, which puts into question the first theory of HF as an infectious disease. Rather than enrichment, beta-diversity measures (inter-individual diversity) revealed a highly significant separation of HF cases and controls, with a significant and specific decrease of *Coriobacteriaceae*, *Erysipelotrichaceae* and *Ruminococcaceae* on the family level. More precisely, *Blautia*, *Collinsella*, uncl. *Erysipelotrichaceae* and uncl. *Ruminococcaceae* showed a significant decrease in HF cases compared to controls on the genus level. Interstingly enough, recent study has demonstrated that *Blautia* might be associated with anti-inflammatory mechanisms, as its intestinal abundance is associated with reduced death and improved overall survival in Graft-versus-Host-Disease [15]. Finally, a reduction in the genus *Faecalibacterium*, a short-chain fatty acid butyrate-producing bacteria, is observed in HF patients. As for Blautia, *Faecalibacterium prausnitzii* was identified as an anti-inflammatory commensal and its reduced abundance was shown to be associated with disrupted on intestinal permeability [16, 17]. It is conceivable that depletion of these genera contributes to HF pathogenesis, since both inflammation and increased intestinal permeability were associated with the pathogenesis of HF. Cui et al. then confirmed that the composition of the intestinal microbiota in HF patients was significantly different from that of the controls, and validated the decrease of *Faecalibacterium prausnitzii* as an essential characteristic of the intestinal microbiota in HF patients [18]. The authors also observed an enrichment in intestinal microbial genes coding for proteins involved in lipopolysaccharide synthesis (highlighting the role of the inflammatory hypothesis resulting from intestinal dysbiosis in the development of HF, discussed below), as well as genes encoding for proteins necessary for the production of the intestinal metabolite, Trimethylamine N-Oxide (discussed below), which has been thought to contribute to the pathogenesis of HF. This characteristic decrease in *Faecalibacterium prausnitzii* has also been demonstrated in elderly patients with HF [19]. Finally, Kummen et al. identified changes in 15 taxons from two cohorts with HF, including a depletion of taxa in the *Lachnospiraceae* family, several of which are known producers of butyrate [20]. Prediction of microbial genes in the merged cohort confirmed low genetic potential for butyrate production in HF microbiomes compared with control subjects, confirming the results obtained by Cui et al. Several taxa of the Lachnospiraceae family were inversely correlated with soluble CD25, a marker for activation of T lymphocytes and macrophages [20]. This discovery again underscores the potential importance of intestinal microbial modulation of inflammation by producing short-chain fatty acids in disease states such as HF.

These studies are the first important steps in the characterization of the gut microbiota profile in HF. However, multiple discrepancies may be noted when comparing the major bacterial groups identified in these studies. As gut microbiota identification methods become more and more standardized and sophisticated, reproducibility must be confirmed in future studies, especially with clinically homogeneous HF cohorts.

2.2 The intestinal barrier dysfunction as a trigger for systemic and cardiac inflammation in HF

Although HF has been recognized as a chronic systemic inflammatory disease, plasma levels of several pro-inflammatory cytokines being associated with both the severity of the disease and poor survival prediction, the origin of this inflammatory state is not yet well understood [21, 22]. Moreover, trials that targeted these cytokines in HF patients failed to show benefit on cardiac function and prognosis [23]. Since, it has been suggested that increased bacterial translocation, i.e. the migration of resident bacteria or bacterial products like endotoxins and lipopolysaccharides from the intestinal lumen to the blood, may be important stimuli for the systemic inflammation occuring during HF. Several mechanisms have been suggested for this increased bacterial translocation,

including structural and functional alterations of the gastrointestinal tract, as well as abnormalities of the immunological defense of the host.

Specifically, HF patients have a decrease in cardiac output leading to congestion and to hypoxia of several terminal organs, including the intestinal wall. This decrease in perfusion particularly affects the villous structure of the intestinal gut wall, leading to the deterioration of the health of the different types of intestinal cells and, consequently, to an impaired integrity of the intestinal barrier. As a result, an increase in paracellular transport in the intestinal epithelium can be observed in HF. HF patients also have a thickened intestinal wall at the terminal ileum and colon, suggesting intestinal edema, and increased collagen accumulation in mucosal of the small intestine. Therefore, these alterations directly contributed to the disrupted integrity of the intestinal barrier and thus to an increase in the intestinal permeability observed in HF. This impaired intestinal barrier function will promote the translocation of bacteria, bacterial fragments, or secreted products into the circulatory system [11, 24–26].

There is now strong evidence validating the bacterial translocation hypothesis in HF. Although a first study has demonstrated dysbiosis in blood microbiota predicts long-term cardiovascular prognosis [27], Dinakaran and colleagues have shown that bacterial 16S rRNA copy number was significantly higher in the plasma, implying the increased presence of cell-free bacterial DNA elements in the circulation of HF patients [28]. At the phylum level, they observed a dominance of Actinobacteria in CVD patients, followed by Proteobacteria, in contrast to that in healthy controls, where Proteobacteria was predominantly enriched, followed by Actinobacteria.

In line with the bacterial translocation hypothesis, higher blood levels of the endotoxin Lipopolysaccharide (LPS), found of the outer membrane of gram-negative bacteria and one of the most potent inducers of proinflammatory cytokine release, were found in patients with decompensated HF [29–31]. This HF-associated endotoxemia was supposed to participate to the systemic inflammation observed in HF. Pathophysiologically relevant amounts of endotoxin have been shown to induce the release of TNF-a, IL-1 and IL-6 from ex vivo whole blood of HF patients [32].

This classic molecule can induce the expression of a wide range of inflammatory products, mainly by the Toll-like receptor 4 (TLR4) pattern recognition receptor, within the heart. This cardiac effect of LPS occurs in many types of cells, such as macrophages, dendritic cells, cardiomyocytes and cardiac fibroblasts. Studies have shown that TLR4 expression increases in the heart of patients with advanced HF [33, 34]. TLR4 is associated with deleterious inflammatory effects that exacerbate cardiac damage, and inhibition of TLR4 reduces the progression of heart failure. Finally, the processes responsible for the increase in intestinal permeability may involve a decrease in the vigilance of the intestinal immune system that would allow, without destroying them, whole bacteria and bacterial components. LPS itself may promote the deterioration of mucosal barrier function [35].

2.3 The gut microbiota-derived metabolites as mediators of HF

Although clinical studies have demonstrated that antibiotics treatment reduced plasma endotoxin levels, an important stimulus for systemic inflammation, in HF patients, decreased plasma cytokine levels have not always been observed, suggesting a prolonged effect. These differences suggested that the gut microbiota may also have an impact on host processes via bioactive metabolites. Through resorption and distribution into the circulatory system, these metabolites can affect the intestinal health, and other functions of the immune system, and the heart, as well.

Of these metabolites, the gut microbiota has been described to interact with the host through a number of pathways, including trimethylamine (TMA) / trimethylamine N-oxide (TMAO) pathway, short-chain fatty acids production, and primary and secondary bile acids. While most bacterial metabolites, which are able to migrate from the intestine to the general circulation, are beneficial to health in normal condition, a decrease in beneficial metabolites-producing bacteria associated with an increase in the production of toxic metabolites, could thus participate in the intestinal and cardiac processes involved in the development of HF.

2.3.1 N-oxyde de triméthylamine (TMAO)

Recent studies have not only revealed a role of TMAO as a promising biomarker for predicting the risk of HF, but also as direct mechanistic link between gut dysbiosis and the development of HF. The TMAO generation is dependent on intestinal microbes and derived from specific dietary nutrients such as choline, phosphatidylcholine and L-carnitine. Initially, Wang and colleagues were the first, in clinical studies, to demonstrate that circulating TMAO levels are higher in patients with HF compared with subjects without HF. TMAO levels were directly correlated with the severity of HF, and associated with unfavorable outcomes in HF patients [36, 37]. TMAO levels were associated with a 3.4-fold increased mortality risk. Since, several groups have replicated these results [38–41]. However, the mechanism explaining why patients with HF have increased levels of TMAO and the mechanism of action of TMAO within the heart remains to be elucidated. Whether manipulation of the gut microbial TMAO pathway, such as through reduction in TMAO levels can attenuate HF, remain to be also determined. Animal model studies suggest that TMAO pathway may directly contribute to the development of HF. Using an experimental model of transverse aortic constriction-induced HF, Organ et al. demonstrated that

ventricular remodeling (including fibrosis, chamber dilatation, LV wall thinning and cardiac function were significantly worse in mice fed a diet containing TMAO when compared with the control diet [42]. These results were confirmed by Li and colleages, demonstrating that TMAO treatment stimulated cardiac hypertrophy and fibrosis in rats. In contrary, reducing TMAO synthesis by antibiotics attenuated TAC-induced cardiac hypertrophy and fibrosis [43]. Recently, 3,3-dimethyl-1-butanol (a trimethylamine formation inhibitor) treatment was shown to reduce TMAO plasma levels, cardiac hypertrophy, lung congestion, left ventricular remodeling and impaired cardiac function in an experimental model of myocardial infarction-induced HF [44].

2.3.2 Short-chain fatty acids (SCFAs)

In contrast, it has also been suggested that the production of many bacterial metabolites promoting cardiovascular benefits may be dysregulated in HF. For example, a connection between microbial SCFAs and HF has also been gathering attention. SCFAs are a major class of bacterial metabolites and are mainly produced in the colon by bacterial fermentation of indigestible fibers. The major SCFAs produced as a result of anaerobic bacterial fermentation of carbohydrates and proteins are acetate, propionate and butyrate, and make up 95% of those found in the body. Although SCFAs are predominantly present in the colon at high concentrations, micromolar levels can also be found in the circulation and have become important signaling molecules with various physiological effects. SCFAs have been shown to be key regulators of ileal motility, production of mucus, and regulation of tight junction protein expression, these factors being critical in maintaining the intestinal barrier integrity. SCFAs have also potent anti-inflammatory effects on immune cell functions in the intestinal tract [45–49]. Although SCFAs may have beneficial effects on all intestinal structural and functional dysfunctions described in HF, there is a limited number of studies examining the direct effects of SCFAs on HF, both in animal and human studies.

Several bacteria have been identified through metagenomic analyses contributing to SCFAs production. Bacteroides, Clostridium, and Bifidobacterium are key acetate producing bacteria while a small group of bacteria including *Faecalibacterium prausnitzii* contribute to a large portion of butyrate production. Both Gram-negative bacteria and gram-positive bacteria are responsible for propionate production. Of interest, as mentioned above, a reduction of the genus *Faecalibacterium prausnitzii* has been consistently observed in HF patients [14, 18, 20]. To date, only one preclinical study try to address the role of SCFAs in the development of HF. In an experimental model of hypertension-induced HF, Marques and colleagues demonstrated that consumption of fiber not only increased the abundance of acetate-producing bacteria, but also reduced cardiac fibrosis and hypertrophy, resulting in a ameliorated cardiac function. Similar results were obtained with a diet supplemented with acetate [50].

2.3.3 Bile acids (BAs)

Bile acids (BAs) are another group of metabolites with a profound effect on human health. Primary BAs are synthesized by the oxidation of cholesterol in the liver. The majority of BAs are reabsorbed in the intestine and returned to the liver to be picked up by the portal vein. However, the microbiota in the colon can further metabolize non-recycled BAs to produce secondary BAs. These secondary BAs also enter the enterohepatic circulation to function as signaling molecules with profound effects on the physiology and pathology of the host. The efffects of BAs are mediated, mainly through two receptors, namely the nuclear farnesyl X receptor (FXR) and the G protein-coupled receptor TGR5. Apart from classic functions of BAs in digestion and solubilization of lipophilic nutrients in the small intestine, recent studies have shown that BAs control inflammation and fibrosis, and restore the intestinal barrier. Further studies have confirmed that FXR activation can reduce intestinal ischemia-reperfusion injury and preserve internal structure and permeability [51, 52].

Since BAs receptors have been described in endothelial cells, fibroblasts, and cardiomyocytes, a potential role of BAs, as signaling molecules, has been proposed top play a direct role in regulating cardiovascular physiology and gut dysbiosis-induced HF [53–55]. To date, the role of BAs in the development of HF remains poorly understood. Although Mayerhofer and colleagues recently demonstrated an increased secondary-to-primary BA ratio in HF patients, as compared to healthy control subjects, no association was found between this increased ratio and the overall survival [56]. In vitro, FXR agonists upregulated cardiomyocyte FXR expression, stimulated myocyte apoptosis, and reduced myocyte viability. Furthermore, levels of FXR were significant increased after myocardial ischaemia/reperfusion, and pharmacological inhibition or genetic ablation of FXR significantly reduced myocardial apoptosis, decreased infarct size, and improved cardiac function. Similar results were obtained recently following chronic myocardial infarction [57]. On the other hand, contradictory results were obtained concerning the TGR5 receptor. Indeed, diets supplemented with cholic acid or a specific TGR5 agonist improved maladaptative ventricular remodeling and contractile dysfunction in the animal model of transverse aortic constriction-induced HF [58]. Furthermore, mice with cardiomyocyte-specific deletion of TGR5 demonstrate increased mortality and exaggerated contractile dysfunction in response to transverse aortic constriction, compared to littermates.

3 Microbiota-targeted therapeutics in heart failure

Both experimental evidence and clinical observations prove the functional links between gut dysbiosis, altered gut metabolites and susceptibility for HF, placing the gut microbiome as a novel and attractive field for therapeutics. Several potential strategies were then suggested, which include dietary regulation, antibiotic intervention, prebiotics, probiotics and faecal microbiota transplantation.

3.1 Dietary and lifestyle changing interventions

Adopting a balanced diet has been described as the most effective way to have a healthy flora, which as, in turn, an essential role in the digestion and absorption of nutrients in the intestine. As such, a diet rich in saturated fat, animal protein and low in fibers, such as the Western diet, is associated with increased intestinal permeability, decreased microbial diversity, proliferation of pathogenic bacteria such as Eubacterium, and increased circulating LPS, etc. This diet is clearly known to increase the risk of HF [59]. Similarly, excessive consumption of L-carnithine, an essential nutrient in red meat, increased gut dysbiosis, plasma concentration of TMAO and accelerated atherosclerosis in mice. This has also been observed in omnivorous humans following ingestion of L-carnitine, compared to vegans or vegetarians, in whom increased plasma TMAO level with concurrently high plasma L-carnithyne concentration were associated with increased risk of HF [60–62]. In contrast, the Mediterranean diet, rich in fruits, vegetables, legumes, whole grains, and low in red meat is described as the diet likely to promote optimal microbial composition favoring a healthy state and decreasing HF incidence up to 74% [63]. In the same way, hypertensive mice fed with high-fibers diet were characterized by and increased abundance of acetate-producing bacteria with amelioration of pathological cardiac remodeling and cardiac dysfunction. Acetate supplementation yielded the same results [50].

Exercise training (ET), a well-known primary prevention tool but also a therapy in HF patients, could be another powerful and promising complementary intervention for health promotion on the intestinal microbiome [64, 65]. Although a direct mechanist link between ET-induced modification in microbiota and HF has not been yet established, Lambert et al. have shown that cecal microbiota from diabetic exercised mice is characterized with higher abundance of Firmicutes species and decreased abundance of Bacteroides and Prevotella species [66]. In the same way, Zhao and colleagues investigated the response of the gut microbiota in amateur half-marathon runners. They demonstrated that abundances of certain microbiota members were significantly different before and after running, especially the family *Coriobacteriaceae*, which was supposed to be a potential biomarker that links exercise with health improvement [67].

Overall, a healthy lifestyle - based on diet and ET- is the best way to prevent and treat various diseases, including HF, through its positive influence on the gut microbiota.

3.2 Antibiotics therapy

One of the most efficient and commonly used experimental strategies for modulating intestinal microbiota, in order to provide mechanistic links between gut dysbiosis and diseases including HF, is the use of antibiotic treatment (Abs). For example, oral vancomycin treatment of Dahl S rats induced smaller left ventricular infarct size, and improved recovery cardiac function following ischemia/reperfusion experiments, as compared with untreated rats [68]. In trials on patients, whether the use of Abs has protective effects against HF remains unanswered and controversial. Conraads and al. demonstrated that Abs treatment, using a coktail of polymixin B and tobramycin, normalized the level of intestinal Gram-negative bacilli in association with a significant decreased of pro-inflammatory cytokines in HF patients. Flow-mediated dilation, as an evidence of endothelial dysfunction, was also significantly improved [69]. However, the observed beneficial effects were limited within the period of treatment. Finally, the potential benefits of Abs need to be weighed against the potential side effects. Polymyxin B has been clinically restricted because of its toxicity. In the same way, macrolides Abs use, one of the most widely used antibiotic groups, was associated with a greater risk of myocardial infarction [70, 71].

3.3 Prebiotics and probiotics therapy

Prebiotics, which are food indigestible molecules that can favor the growth of beneficial microbial organisms, or probiotics, defined as live microorganisms, are also interesting therapeutic strategies to restore a healthy flora in order to provide a health benefit to the host. Although the potential beneficial effects of prebiotics in the setting of HF are limited, a high-fiber diet has been recently shown to lower gut dysbiosis (evaluated by the ratio between Firmicutes and Bacteroidetes), decreased blood pressure, normalized cardiac hypertrophy and improved cardiac function in an experimental model of hypertention-induced HF [50]. Accumulating evidence has also demonstrated that probiotics can favorably modulate cardiac remodeling and function in HF [72]. It has been reprted that oral administration of Goodbelly, containing the bacteria *Lactobacillus plantarum* 299v, induced cardioprotective effects, including smaller left ventricular infarct size and improved cardiac function following myocardial ischemia/reperfusion, in rats [67]. Similar results were obtained using *Lactobacillus rhamnosus* GR-1 [73]. Probiotic therapy has been recently tested in HF patients. Costanza et al.

demonstrated that HF patients treated with *S. boulardii* for 3-months presented a reduction on biochemical and inflammatory biomarkers, and also an improvement on cardiac systolic function, compared with placebo group [74]. A similar study, using *Lactobacillus rhamnosus* is under investigation [75].

3.4 Faecal microbiota transplantation (FMT)

Interest in the therapeutic potential of faecal microbiota transplant (FMT), aiming at transfering a healthy flora into diseased receiver, has been increasing globally in recent years [9]. This approach has been proven to be mosly effective in the treatment of *Clostridium difficile* infection [76]. However, to date, no study has been realized in the setting of HF. Nevertheless, it could be hypothesized that the FMT strategy will be more effective than Abs or probiotics approaches, since a recent study demonstrated, that FMT induced a more efficient recovery of intestinal microbiome than a mixture of probiotics in mice pre-treated with antibiotics [77].

4 Conclusion

In summary, over the last decade, an evident association has been demonstrated between gut dysbiosis and HF. Of the gut-derived metabolites, only a mechanistic link between TMAO to HF has been demonstrated in animal and human studies. Further studies, focusing on a greater mechanistic understanding of the gut microbiome and/or microbiota-derived metabolites in the pathogenesis of HF, are necessary to develop novel therapeutic strategies.

Funding information This work was supported by INSERM. Rémy Burcelin has received grants from Fondation de France (grant number 201300038591).

Compliance with ethical standards

Conflict of interest M. Branchereau declares that he has no conflict of interest. R. Burcelin declares that he has no conflict of interest. C. Heymes declares that he has no conflict of interest.

Human or animals participants This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the global burden of disease study 2015. Lancet. 2016;388(10053):1459–544.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. American College of Cardiology Foundation/American Heart Association task force on practice guidelines. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation. 2013;128(16):e240–327.
3. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, et al. American Heart Association statistics committee and stroke statistics subcommittee. Heart disease and stroke statistics–2013 update: a report from the American Heart Association. Circulation. 2013;127(1):e6–e245.
4. Hooper LV, Gordon JI. Commensal host-bacterial relationships in the gut. Science. 2001;292(5519):1115–8.
5. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014;157(1):121–41.
6. Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. Nat Rev Immunol. 2013;13(11):790–801.
7. Levy M, Kolodziejczyk AA, Thaiss CA, Elinav E. Dysbiosis and the immune system. Nat Rev Immunol. 2017;17(4):219–32.
8. Nagatomo Y, Tang WH. Intersections between microbiome and heart failure: revisiting the gut hypothesis. J Card Fail. 2015;21(12):973–80.
9. Tang WH, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. Circ Res. 2017;120(7):1183–96.
10. Tang WHW, Li DY, Hazen SL. Dietary metabolism, the gut microbiome, and heart failure. Nat Rev Cardiol. 2019;16(3):137–54.
11. Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol. 2007;50(16):1561–9.
12. Sandek A, Swidsinski A, Schroedl W, Watson A, Valentova M, et al. Intestinal blood flow in patients with chronic heart failure: a link with bacterial growth, gastrointestinal symptoms, and cachexia. J Am Coll Cardiol. 2014;64(11):1092–102.
13. Pasini E, Aquilani R, Testa C, Baiardi P, Angioletti S, et al. Pathogenic gut Flora in patients with chronic heart failure. JACC Heart Fail. 2016;4(3):220–7.
14. Luedde M, Winkler T, Heinsen FA, Rühlemann MC, Spehlmann ME, et al. Heart failure is associated with depletion of core intestinal microbiota. ESC Heart Fail. 2017;4(3):282–90.
15. Jenq RR, Taur Y, Devlin SM, Ponce DM, Goldberg JD, et al. Intestinal Blautia is associated with reduced death from graft-versus-host disease. Biol Blood Marrow Transplant. 2015;21(8):1373–83.
16. Miquel S, Martín R, Rossi O, Bermúdez-Humarán LG, Chatel JM, et al. Faecalibacterium prausnitzii and human intestinal health. Curr Opin Microbiol. 2013;16(3):255–61.
17. Richard ML, Sokol H. The gut mycobiota: insights into analysis, environmental interactions and role in gastrointestinal diseases. Nat Rev Gastroenterol Hepatol. 2019;16(6):331–45.
18. Cui X, Ye L, Li J, Jin L, Wang W, et al. Metagenomic and metabolomic analyses unveil dysbiosis of gut microbiota in chronic heart failure patients. Sci Rep. 2018;8(1):635.
19. Kamo T, Akazawa H, Suda W, Saga-Kamo A, Shimizu Y, et al. Dysbiosis and compositional alterations with aging in the gut microbiota of patients with heart failure. PLoS One. 2017;12(3):e0174099.
20. Kummen M, Mayerhofer CCK, Vestad B, Broch K, Awoyemi A, et al. Gut microbiota signature in heart failure defined from profiling of 2 independent cohorts. J Am Coll Cardiol. 2018;71(10):1184–6.
21. Pullen AB, Jadapalli JK, Rhourri-Frih B, Halade GV. Re-evaluating the causes and consequences of non-resolving inflammation in chronic cardiovascular disease. Heart Fail Rev. 2019; In press.
22. Sarhene M, Wang Y, Wei J, Huang Y, Li M, et al. Biomarkers in heart failure: the past, current and future. Heart Fail Rev. 2019; In press.

23. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the randomized Etanercept worldwide evaluation (RENEWAL). Circulation. 2004;109(13):1594–602.
24. Sandek A, Anker SD, von Haehling S. The gut and intestinal bacteria in chronic heart failure. Curr Drug Metab. 2009;10(1):22–8.
25. Krack A, Richartz BM, Gastmann A, Greim K, Lotze U, et al. Studies on intragastric PCO2 at rest and during exercise as a marker of intestinal perfusion in patients with chronic heart failure. Eur J Heart Fail. 2004;6(4):403–7.
26. Arutyunov GP, Kostyukevich OI, Serov RA, Rylova NV, Bylova NA. Collagen accumulation and dysfunctional mucosal barrier of the small intestine in patients with chronic heart failure. Int J Cardiol. 2008;125(2):240–5.
27. Amar J, Lange C, Payros G, Garret C, Chabo C, et al. Blood microbiota dysbiosis is associated with the onset of cardiovascular events in a large general population: the D.E.S.I.R. study. PLoS One. 2013;8(1):e54461.
28. Dinakaran V, Rathinavel A, Pushpanathan M, Sivakumar R, Gunasekaran P, et al. Elevated levels of circulating DNA in cardiovascular disease patients: metagenomic profiling of microbiome in the circulation. PLoS One. 2014;9(8):e105221.
29. Niebauer J, Volk HD, Kemp M, Dominguez M, Schumann RR, et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. Lancet. 1999;353(9167):1838–42.
30. Peschel T, Schönauer M, Thiele H, Anker SD, Schuler G, et al. Invasive assessment of bacterial endotoxin and inflammatory cytokines in patients with acute heart failure. Eur J Heart Fail. 2003;5(5):609–14.
31. Sandek A, Bjarnason I, Volk HD, Crane R, Meddings JB, et al. Studies on bacterial endotoxin and intestinal absorption function in patients with chronic heart failure. Int J Cardiol. 2012;157(1):80–5.
32. Conraads VM, Bosmans JM, Schuerwegh AJ, Goovaerts I, De Clerck LS. At al. Intracellular monocyte cytokine production and CD 14 expression are up-regulated in severe vs mild chronic heart failure. J Heart Lung Transplant. 2005;24(7):854–9.
33. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. Nat Rev Cardiol. 2014;11(5):255–65.
34. Yu L, Feng Z. The role of toll-like receptor signaling in the progression of heart failure. Mediat Inflamm. 2018;2018:9874109.
35. Hietbrink F, Besselink MG, Renooij W, de Smet MB, Draisma A, et al. Systemic inflammation increases intestinal permeability during experimental human endotoxemia. Shock. 2009;32(4):374–8.
36. Tang WH, Wang Z, Fan Y, Levison B, Hazen JE, et al. Prognostic value of elevated levels of intestinal microbe-generated metabolite trimethylamine-N-oxide in patients with heart failure: refining the gut hypothesis. J Am Coll Cardiol. 2014;64(18):1908–14.
37. Tang WH, Wang Z, Shrestha K, Borowski AG, Wu Y, et al. Intestinal microbiota-dependent phosphatidylcholine metabolites, diastolic dysfunction, and adverse clinical outcomes in chronic systolic heart failure. J Card Fail. 2015;21(2):91–6.
38. Albert CL, Tang WHW. Metabolic biomarkers in heart failure. Heart Fail Clin. 2018;14(1):109–18.
39. Hayashi T, Yamashita T, Watanabe H, Kami K, Yoshida N, et al. Gut microbiome and plasma microbiome-related metabolites in patients with decompensated and compensated heart failure. Circ J. 2018;83(1):182–92.
40. Suzuki T, Yazaki Y, Voors AA, Jones DJL, Chan DCS, et al. Association with outcomes and response to treatment of trimethylamine N-oxide in heart failure (from BIOSTAT-CHF). Eur J Heart Fail. 2018; In press.
41. Kanitsoraphan C, Rattanawong P, Charoensri S, Senthong V. Trimethylamine N-oxide and risk of cardiovascular disease and mortality. Curr Nutr Rep. 2018;7(4):207–13.
42. Organ CL, Otsuka H, Bhushan S, Wang Z, Bradley J, et al. Choline diet and its gut microbe-derived metabolite, trimethylamine N-oxide, exacerbate pressure overload-induced heart failure. Circ Heart Fail. 2016;9(1):e002314.
43. Li Z, Wu Z, Yan J, Liu H, Liu Q, et al. Gut microbe-derived metabolite trimethylamine N-oxide induces cardiac hypertrophy and fibrosis. Lab Investig. 2019;99(3):346–57.
44. Li X, Sun Y, Zhang X, Wang J. Reductions in gut microbiota-derived metabolite trimethylamine N-oxide in the circulation may ameliorate myocardial infarction-induced heart failure in rats, possibly by inhibiting interleukin-8 secretion. Mol Med Rep. 2019; In press.
45. Blacher E, Levy M, Tatirovsky E, Elinav E. Microbiome-modulated metabolites at the Interface of host immunity. J Immunol. 2017;198(2):572–80.
46. Levy M, Blacher E, Elinav E. Microbiome, metabolites and host immunity. Curr Opin Microbiol. 2017;35:8–15.
47. Tang WHW, Bäckhed F, Landmesser U, Hazen SL. Intestinal microbiota in cardiovascular health and disease: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73(16):2089–105.
48. Battson ML, Lee DM, Weir TL, Gentile CL. The gut microbiota as a novel regulator of cardiovascular function and disease. J Nutr Biochem. 2018;56:1–15.
49. Wang Z, Zhao Y. Gut microbiota derived metabolites in cardiovascular health and disease. Protein Cell. 2018;9(5):416–31.
50. Marques FZ, Nelson E, Chu PY, Horlock D. Fiedler et al. high-Fiber diet and acetate supplementation change the gut microbiota and prevent the development of hypertension and heart failure in hypertensive mice. Circulation. 2017;135(10):964–77.
51. Lefebvre P, Cariou B, Lien F, Kuipers F, Staels B. Role of bile acids and bile acid receptors in metabolic regulation. Physiol Rev. 2009;89(1):147–91.
52. Wahlström A, Sayin SI, Marschall HU, Bäckhed F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metab. 2016;24(1):41–50.
53. Hanafi NI, Mohamed AS, Sheikh Abdul Kadir SH, Othman MHD. Overview of bile acids signaling and perspective on the signal of Ursodeoxycholic acid, the most hydrophilic bile acid, in the heart. Biomolecules. 2018;8(4):e159.
54. Khurana S, Raufman JP, Pallone TL. Bile acids regulate cardiovascular function. Clin Transl Sci. 2011;4(3):210–8.
55. Vasavan T, Ferraro E, Ibrahim E, Dixon P, Gorelik J, et al. Heart and bile acids - clinical consequences of altered bile acid metabolism. Biochim Biophys Acta Mol basis Dis. 2018;1864(4 Pt B):1345–55.
56. Mayerhofer CCK, Ueland T, Broch K, Vincent RP, Cross GF, et al. Increased secondary/primary bile acid ratio in chronic heart failure. J Card Fail. 2017;23(9):666–71.
57. Gao J, Liu X, Wang B, Xu H, Xia Q, et al. Farnesoid X receptor deletion improves cardiac function, structure and remodeling following myocardial infarction in mice. Mol Med Rep. 2017;16(1):673–9.
58. Eblimit Z, Thevananther S, Karpen SJ, Taegtmeyer H, Moore DD, et al. TGR5 activation induces cytoprotective changes in the heart and improves myocardial adaptability to physiologic, inotropic, and pressure-induced stress in mice. Cardiovasc Ther. 2018;36(5):e12462.
59. Battson ML, Lee DM, Jarrell DK, Hou S, Ecton KE, et al. Suppression of gut dysbiosis reverses Western diet-induced vascular dysfunction. Am J Physiol Endocrinol Metab. 2018;314(5):E468–77.
60. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19(5):576–85.
61. Koeth RA, Lam-Galvez BR, Kirsop J, Wang Z, Levison BS, et al. L-carnitine in omnivorous diets induces an atherogenic gut microbial pathway in humans. J Clin Invest. 2019;129(1):373–87.

62. Lang JM, Pan C, Cantor RM, Tang WHW, Garcia-Garcia JC, Kurtz I, Hazen SL, Bergeron N, Krauss RM, Lusis AJ. Impact of individual traits, saturated fat, and protein source on the gut microbiome. MBio. 2018;9(6):e01604–18.
63. Lopez-Garcia E, Rodriguez-Artalejo F, Li TY, Fung TT, Li S, et al. The Mediterranean-style dietary pattern and mortality among men and women with cardiovascular disease. Am J Clin Nutr. 2014;99(1):172–80.
64. Bjarnason-Wehrens B, Nebel R, Jensen K, Hackbusch M, Grilli M, et al. German Society of Cardiovascular Prevention and Rehabilitation (DGPR). Exercise-based cardiac rehabilitation in patients with reduced left ventricular ejection fraction: the cardiac rehabilitation outcome study in heart failure (CROS-HF): a systematic review and meta-analysis. Eur J Prev Cardiol. 2019. https://doi.org/10.1177/2047487319854140.
65. Mailing LJ, Allen JM, Buford TW, Fields CJ, Woods JA. Exercise and the gut microbiome: a review of the evidence, potential mechanisms, and implications for human health. Exerc Sport Sci Rev. 2019;47(2):75–85.
66. Lambert JE, Myslicki JP, Bomhof MR, Belke DD, Shearer J, et al. Exercise training modifies gut microbiota in normal and diabetic mice. Appl Physiol Nutr Metab. 2015;40(7):749–52.
67. Zhao X, Zhang Z, Hu B, Huang W, Yuan C, Zou L. Response of gut microbiota to metabolite changes induced by endurance exercise. Front Microbiol. 2018;9:765.
68. Lam V, Su J, Koprowski S, Hsu A, Tweddell JS, et al. Intestinal microbiota determine severity of myocardial infarction in rats. FASEB J. 2012;26(4):1727–35.
69. Conraads VM, Jorens PG, De Clerck LS, Van Saene HK, et al. Selective intestinal decontamination in advanced chronic heart failure: a pilot trial. Eur J Heart Fail. 2004;6(4):483–91.
70. Cheng YJ, Nie XY, Chen XM, Lin XX, Tang K, et al. The role of macrolide antibiotics in increasing cardiovascular risk. J Am Coll Cardiol. 2015;66(20):2173–84.
71. Gorelik E, Masarwa R, Perlman A, Rotshild V, Muszkat M, et al. Systemic review, meta-analysis, and network meta-analysis of the cardiovascular safety of macrolides. Antimicrob Agents Chemother. 2018;62(6):e00438–18.
72. Ettinger G, MacDonald K, Reid G, Burton JP. The influence of the human microbiome and probiotics on cardiovascular health. Gut Microbes. 2014;5(6):719–28.
73. Gan XT, Ettinger G, Huang CX, Burton JP, Haist JV, et al. Probiotic administration attenuates myocardial hypertrophy and heart failure after myocardial infarction in the rat. Circ Heart Fail. 2014;7:491–9.
74. Costanza AC, Moscavitch SD, Faria Neto HC, Mesquita ET. Probiotic therapy with Saccharomyces boulardii for heart failure patients: a randomized, double-blind, placebo-controlled pilot trial. Int J Cardiol. 2015;179:348–50.
75. Mayerhofer CCK, Awoyemi AO, Moscavitch SD, Lappegård KT, Hov JR, et al. Design of the GutHeart-targeting gut microbiota to treat heart failure-trial: a phase II, randomized clinical trial. ESC Heart Fail. 2018;5(5):977–84.
76. Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. J Clin Gastroenterol. 2014;48(8):693–702.
77. Suez J, Zmora N, Zilberman-Schapira G, Mor U, Dori-Bachash M, et al. Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. Cell. 2018;174(6):1406–1423.e16.