Review Articles

Intersections Between Microbiome and Heart Failure: Revisiting the Gut Hypothesis

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ABSTRACT

Microbes play an important role in human health and disease. In the setting of heart failure (HF), substantial hemodynamic changes, such as hypoperfusion and congestion in the intestines, can alter gut morphology, permeability, function, and possibly the growth and composition of gut microbiota. These changes can disrupt the barrier function of the intestines and exacerbate systemic inflammation via microbial or endotoxin translocation into systemic circulation. Furthermore, cardiorenal alterations via metabolites derived from gut microbiota can potentially mediate or modulate HF pathophysiology. Recently, trimethylamine *N*-oxide (TMAO) has emerged as a key mediator that provides a mechanistic link between gut microbiota and multiple cardiovascular diseases, including HF. Potential intervention strategies which may target this microbiota-driven pathology include dietary modification, prebiotics/probiotics, and selective binders of microbial enzymes or molecules, but further investigations into their safety and efficacy are warranted. (*J Cardiac Fail 2015;21:973−980*)

Key Words: Microbiome, TMAO, heart failure.

There is growing literature to support a role of the gut in the pathogenesis of heart failure (HF) in what is often referred to as the ''gut hypothesis of heart failure.'' The gut hypothesis implies that decreased cardiac output and redistribution of systemic circulation can lead to a decrease in intestinal perfusion, mucosal ischemia, and ultimately a disrupted intestinal mucosa. This disruption in intestinal barrier function in turn can lead to increased gut permeability, increased bacterial translocation, and increased circulating endotoxins which can contribute to the underlying inflammation seen in patients with HF. With new insights into the role of gut microbiota in health and disease, the contribution of gut microbiota and its metabolites have broadened the scope of the gut hypothesis. Herein, we summarize the evidence regarding the intricate interaction between intestine and heart in the setting of HF, as well as the association of gut microbiota with HF. We also discuss some key molecules derived from gut microbiota and potential pathogenic mechanisms that may be relevant to HF. Although approaches to modulating gut microbiota to treat HF are not yet established, possible intervention strategies aimed at these novel potential therapeutic targets are currently under active investigation.

Gut Microbiota in Health and Disease

There are $\sim 10^{14}$ bacterial organisms belonging to $>2{,}000$ species within our bodies, the vast majority being in the gut.[1] These are commensal microorganisms that colonize in the human gut and play a crucial role in protection from environmental exposure, digestion, and absorption of nutrients.[2−4] The phylogenetic composition of the bacterial communities evolves toward an adult-like

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configuration during the 1st few years of life. The shaping of gut microbiota is largely influenced by lifestyle factors and/or environmental exposure rather than by inherited genetic factors.[5]

There is increasing evidence that the nature of the microbiome plays an important role in human health and disease. Recent development of high-throughput assays, such as next-generation sequencing analysis of bacterial 16S ribosomal DNA, has made it possible to explore the composition of huge numbers of diverse microbiota in the gut in humans and other animals.[5–8] Numerous studies have shown alterations of gut microbiota in a variety of conditions or diseases, such as obesity,[7,9] fatty liver, insulin resistance,[10] diabetes mellitus,[8] and hypertension.[11] Experiments in fecal transplantation from conventionally raised animals to germ-free or microbiota-ablated ones have shown that these lifestyle alterations contribute, at least in part, to the pathogenesis of these diseases.[7–11]

Gut Microbiota and Heart Failure

Alteration of Gut and Gut Microbiota in Heart Failure

The gut is a blood-demanding organ, and villi (and microvilli) are prone to functional ischemia due to reduced blood flow.[12] The arteries form dense capillary networks close to the top of the villi. This anatomic arrangement allows countercurrent exchange of oxygen from the arteries to the veins along their course within the villus. This results in a descending gradient of tissue oxygen concentration from the base to the tip of the villus. This gradient is inversely related to blood flow[12]; therefore, it is directly influenced by alterations in perfusion in the context of HF. In patients with HF, intestinal ischemia can be demonstrated by a decrease in intestinal mucosal pH[13] or diminished passive carrier-mediated transport of D-xylose.[14] Possibly as a result of intestinal ischemia[12,15] and congestion,[16] the morphology, permeability, and function of the intestines are substantially altered in HF, especially in advanced stages with cardiac cachexia.[14,17,18] In fact, the increase in bowel wall thickness due to edema can be directly visualized in patients with HF.[17]

The mechanistic links between gut microbiota and HF are becoming better known. Although evidence is still accruing, higher concentrations of adherent bacteria have been identified in the intestinal mucosal biofilm of patients with HF compared with control subjects.[17] Because gut luminal hypoxia, hypercapnia, changes in local pH, redox state, and norepinephrine are all known to be potent activators of bacterial virulence in microbiota,[19] the composition of intestinal microbiota may shift rapidly during intestinal ischemia and reperfusion[20] or following an increase in portal vein pressure.[21] Hypoperfusion and congestion in intestine owing to reduced cardiac output can further disrupt the barrier function of the intestine and can promote systemic inflammation through bacterial translocation, potentially leading to further HF exacerbations (Fig. 1). However, major changes in the gut microbial composition have not been observed in nonhuman animal models of HF, such as one induced by coronary artery ligation in the rat.[22] In this regard, there is a paucity of data regarding altered gut microbial composition that is unique to human HF.

Systemic Inflammation Caused by Bacterial Translocation

Even though the levels of circulating proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) are elevated in HF,[23–28] trials that targeted these cytokines in patients with HF failed to show benefit in cardiac function or prognosis.[29] Alternatively, it has been proposed that endotoxins may be an important stimulus for cytokine production in patients with HF through their action on mononuclear cells.[24] Bacteria or bacterial endotoxins, such as lipopolysaccharide (LPS), can enter the mesenteric lymph nodes or the systemic circulation through the intestine if its barrier function is impaired, as is the case in various diseases, such as multiple organ failure, sepsis, liver cirrhosis, ischemia reperfusion, or burn injury.[30–33] The mechanism that leads to bacterial translocation from the gut to systemic circulation in the setting of HF can be explained by impaired host defense[34] as well as alterations in gut microbiota and intestinal barrier function that can be induced by hemodynamic changes in the intestines.[15,20,21,35]

There is evidence that bacteria or endotoxins are translocated into systemic circulation in humans in the absence of systemic or local infections. Indeed, bacterial DNA can be commonly detected in systemic circulation in the general population,[36,37] although the origins of these bacterial DNA remain unknown. Higher concentrations of bacterial DNA have been quantified in patients with heart disease compared with healthy subjects, and even the compositions of the bacteria were different between these groups.[38] It has therefore been proposed that the concentration of bacterial DNA and its composition had a considerable impact on the onset of cardiovascular events.[37] In fact, levels of endotoxin and inflammatory markers (IL-6, TNF-α, and soluble TNF receptor 1) increased during acute cardiac decompensation and endotoxin levels decreased after stabilization.[14,39,40] Furthermore, endotoxin levels were higher in the hepatic veins compared with the left ventricle (LV) or pulmonary artery, suggesting possible endotoxin translocation from the gut into the circulation.[40] Moreover, selective eradication of intestinal aerobic gram-negative bacilli with the use of enteral nonabsorbable polymyxin B resulted in a decrease in fecal endotoxin concentrations, monocyte production of some proinfammatory cytokines in patients with HF, and improved flow-mediated dilation, a marker of endothelial function.[41] These findings provide proof of concept that the gut microbiota can affect the systemic inflammatory response in patients with HF, even though this may not translate into substantial changes in circulating endotoxin or proinflammatory cytokine levels.[41]