The role of gut dysbiosis-associated inflammation in heart failure

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INTRODUCTION

Heart failure (HF) is an important public health problem, with high mortality and morbidity. Its prevalence has increased due to the aging of the population, once the disease affects approximately 1–2% of the adult population in developed countries, rising to more than 10% among people over 70 years of age. In Brazil, according to DATASUS, an organ of the Ministry of Health, more than 26000 patients died due to HF in 2012$^1$.

HF patients are recognized by a progressive increase in congestion that is associated with an elevation of circulating biomarkers of inflammation, a condition that is associated with impairment in functional capacity and predicts poor clinical outcomes. Inflammation in HF patients is a frequent condition, contributing to the pathogenesis and progression of the disease through diverse mechanistic pathways that culminate with increased levels of pro-inflammatory cytokines, especially interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α)$^2$.

Although inflammation is a common condition in HF patients, it is still poorly understood what the origin of the inflammatory process in these patients is$^3$. Recent evidence suggested that gut microbiome plays a major role in both health maintenance and disease. The imbalance of microbial communities in the gut, named gut dysbiosis, seems to be a potential contributor to HF progression by activating inflammatory pathways$^4$.

Thus, the possible cross talk between gut dysbiosis and HF severity is intriguing and has the potential to identify new pathways and treatment strategies for HF. So, the aim of this revision was to clarify the possible association of gut dysbiosis, inflammation, and HF, and possible diagnosis, prevention, and treatment strategies.

Gut microbiota

The human gut microbiota is a complex ecological community that has likely coevolved with humans for millions of years, resulting in reciprocal physiological changes. The colonization of gut bacteria begins at birth and gradually becomes more diverse by 2–3 years of age, when it begins to resemble the adult gut microbiota$^4$. It has been established that $>10^{14}$ (>100 trillion) microorganisms (e.g., bacteria, archaea, yeast, and viruses) inhabit the human intestine, with differences in numbers of microbes and microbiota composition along the digestive tract$^5$.

At the moment, four main bacterial phyla have been identified in the human gut: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, with the phyla Firmicutes and Bacteroidetes being the most characteristic in the healthy gut (>90%)$^4$. However, the composition of human microbiota is subjected to a number of changes during health and disease, being influenced by stress, diet, exercise, disease, and medications, and becoming less diverse again toward extreme old age$^4,6$.

Thus, the effect of gut microbiota on host physiology is not limited to processing food nutrients otherwise indigestible, but promotes the host's health in a number of other ways, which include a local protective function regulating mucosal barriers and the immune system preventing the proliferation of pathogens$^5$. Therefore, the effects of gut flora on host metabolism and immunity might be considered a key mechanism in human physiology.

Gut dysbiosis and HF severity

Gut dysbiosis has generally been described as a significant deviation from the functional microbiome$^4$. Each of the following three conditions can be considered as dysbiosis:

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(A) loss of valuable microbial organisms,
(B) expression of pathobionts of possibly beneficial microorganisms, and
(C) loss of general microbial variety7.

The literature already describes the possible association between gut dysbiosis and the manifestation or worsening of several diseases, e.g., HF4,8.

HF is a disease characterized by a state of chronic inflammation with elevated circulating levels of pro-inflammatory cytokines, such as TNF-α, as originally described by Levine et al. in 19909. These circulating cytokines act as cardioprotectors via different pathways that include alterations in myocardial intracellular calcium homeostasis, reduction in mitochondrial activity, and alterations in matrix metalloproteinase expression, resulting in an adverse response from myocardial, which includes negative inotropism, cardiomyocyte hypertrophy, and apoptosis10. However, the origin of inflammation in patients with HF is still controversial and includes different hypotheses, highlighting a decrease in intestinal perfusion and mucosal ischemia, resulting in gut disruption with increased gut permeability, and subsequently enhancing the translocation of bacteria and bacterial toxins in the blood, which can contribute to systemic inflammation and then to HF exacerbations10,11.

The intestinal epithelium acts as an impervious barrier to prevent lipopolysaccharide (LPS) translocation. However, in a dysbiosis condition, the intestinal barrier increases in permeability as a result of a disruption to the regulation of the epithelial cell-to-cell tight junction protein network. A compromised intestinal barrier can be associated with bacterial translocation from the gut into the systemic circulation increasing the risk of inflammation and metabolic endotoxemia (ME), and may represent an important mediator of low-grade systemic inflammation12. Figure 1 summarizes the possible relationship between gut dysbiosis and HF.

LPS is the major component of the outer membrane of Gram-negative bacteria. Under septic circumstances, circulating LPS acts as a pathogen-associated molecular pattern, being able to stimulate the innate immune system, mediating a local or systemic inflammatory response. LPS can also stimulate nonimmune cells and initiate the inflammatory process. The literature reports that an innate LPS-pattern recognition receptor, the Toll-like receptor-4 (TLR-4) is widely expressed in the body, including cardiac tissue13. Thus, the innate inflammatory response can be induced in cardiomyocytes by LPS independently of the immune cell involvement14.

Biomarkers of intestinal dysbiosis
Given the relevance of gut-associated inflammation in HF patients, the early identification of this condition is fundamental for the treatment and aggravation of this disease15. Thus, in the face of dysbiosis, some metabolites, including N-oxide-trimethylamine (TMAO), short-chain fatty acids (SCFAs), circulating LPS, and zonulin primary and secondary bile acid, are generated and may act as biomarkers of intestinal dysbiosis, predicting inflammation in HF16.

TMAO is a urine toxin stimulated by choline, phosphatidylcholine, and L-carnitine fermentation that occurs biologically in the intestinal microbiota17. However, in conditions of gut dysbiosis, the levels of TMAO are elevated in the circulation, which can contribute to the severity of heart disease, especially by stimulating chronic inflammation18. The literature reports that increased levels of TMAO contribute to overexpression of pro-inflammatory cytokines, such as TNF-α and IL-1β, and also the attenuation of anti-inflammatory cytokines such as IL-1019. Recent evidence has suggested the TMAO level as a biomarker to assess gut barrier permeability19.

Zonulin is a family peptide produced in the intestinal and hepatic cells that regulate a protein complex named tight junctions. The literature has reported that high levels of zonulin are associated with increased intestinal permeability20, a condition that allows the translocation of LPS from the intestinal lumen into circulation, resulting in endotoxemia and a low-grade chronic inflammation through the activation of Toll-like receptors21.

The SCFAs acetate, propionate, and butyrate are the main metabolites produced in the colon by bacterial fermentation of dietary fibers and resistant starch, exerting effects on the colon as energy supply and trophic factors22. SCFAs improve gut health through a number of local effects, ranging from maintenance of intestinal barrier integrity, mucus production, to protection against inflammation23. Higher fecal SCFAs are also associated with central obesity, hypertension, and subclinical measures of cardiometabolic disease (e.g., inflammation, glycemia, and dyslipidemia)24.

LPS is the major component of the outer membrane of Gram-negative bacteria. Increased gut permeability enhances the penetration of gut microbiota-derived LPS from the intestine into the bloodstream25. High levels of serum LPS have been associated with pathological processes, including diabetes, the progression of kidney disease, obesity, and inflammation. LPS induces inflammation via a cascade of inflammatory responses following the recognition of lipid A by immune cells. Lipid A is the toxic component of LPS and serves as the microbe-specific molecular signal that binds to the surface receptor complexes of immune cells, which comprise TLR-426.
Modulation of dysbiosis as a potential target in heart failure

Once dysbiosis may contribute to the pathogenesis and progression of HF, modulation of this condition could be an effective therapeutic target. Among the main interventions, the literature reports diet modification, including high intake of fruits and vegetables and low consumption of red meat and simple carbohydrate, is well-documented26.

Probiotics are live beneficial bacteria that re-establish an appropriate intestinal balance by different mechanisms, including pH modulation, antibacterial compound production, and competition with pathogens. Probiotics mainly include bifidobacteria, yeasts, and lactic acid bacteria26,27. Prebiotics are non-digestible carbohydrates used as fermentation substrates and stimulate the proliferation and activity of beneficial intestinal bacteria. It includes oligofructose administered26,27.

Figure 1. Relationship between gut dysbiosis and heart failure. Under health conditions, gut mucosa has normal tight junctions and works as an immunological barrier. In dysbiosis, mucosa becomes permeable and the levels of lipopolysaccharide and N-oxide-trimethylamine increase. This condition induces an inflammatory response by Toll-like receptor-4 activation, resulting in negative inotropism and cardiomyocyte hypertrophy and apoptosis.
by supplements or consumed in foods, such as asparagus, sugar beet, garlic, chicory, onion, banana, etc. 28.  

Fecal microbiota transplantation (FMT) is a method of treating intestinal microecological imbalance and reconstructing normal intestinal function by introducing bacteria or metabolites from donor feces into diseased receptors. It is used to treat *Clostridium difficile*. There are no clinical studies that evaluate FMT in HF patients 27. There are no clinical studies that evaluate FMT in HF patients 27.  

Antibiotic treatment destroys the balance of intestinal flora, leading to a decrease in flora abundance and changes in composition 29. It is important to emphasize that improper use of antibiotics can kill beneficial bacteria in the body, making pathogens resistant and causing various adverse reactions. Thus, the positive and negative effects of the use of antibiotics have to be considered.

FMT in HF patients 27.  

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