REVIEW ARTICLE

https://doi.org/10.1590/1806-9282.20220197

The role of gut dysbiosis-associated inflammation in heart failure

Fabiane Valentini Francisqueti-Ferron[1,2*], Erika Tiemi Nakandakare-Maia[1,3], Juliana Silva Siqueira[1], Artur Junio Togneri Ferron[1,2], Taynara Aparecida Vieira[1], Silméia Garcia Zanati Bazan[1], Camila Renata Corrêa[1]

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 DATA-SUS, 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 P*roteobacteria*, with the phyla *Firmicutes* and *Bacteroidetes* being the most characteristic in the healthy gut (>90%)[5]. 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:

[1]Universidade Estadual Paulista "Júlio de Mesquita Filho", Medical School – Botucatu (SP), Brazil.
[2]Faculdades Integradas de Bauru – Bauru (SP), Brazil.
[3]Centro Universitário Sudoeste Paulista – Avaré (SP), Brazil.
*Corresponding author: fabiane_vf@yahoo.com.br
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 28, 2022. Accepted on June 02, 2022.

(A) loss of valuable microbial organisms,
(B) expression of pathobionts of possibly beneficial microorganisms, and
(C) loss of general microbial variet1y[7].

The literature already describes the possible association between gut dysbiosis and the manifestation or worsening of several diseases, e.g., HF[4,8].

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 1990[9]. These circulating cytokines act as cardiosuppressors 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 apoptosis[10]. 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 exacerbations[10,11].

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 inflammation[7,12]. 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 tissue[13]. Thus, the innate inflammatory response can be induced in cardiomyocytes by LPS independently of the immune cell involvement[14].

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 disease[15]. 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 HF[16].

TMAO is a urine toxin stimulated by choline, phosphatidylcholine, and L-carnitine fermentation that occurs biologically in the intestinal microbiota[17]. 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 inflammation[7]. 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-10[18]. Recent evidence has suggested the TMAO level as a biomarker to assess gut barrier permeability[19].

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 permeability[20], 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 receptors[21].

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 factors[22]. SCFAs improve gut health through a number of local effects, ranging from maintenance of intestinal barrier integrity, mucus production, to protection against inflammation[22]. Higher fecal SCFAs are also associated with central obesity, hypertension, and subclinical measures of cardiometabolic disease (e.g., inflammation, glycemia, and dyslipidemia)[23].

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 bloodstream[24]. 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-4[25].

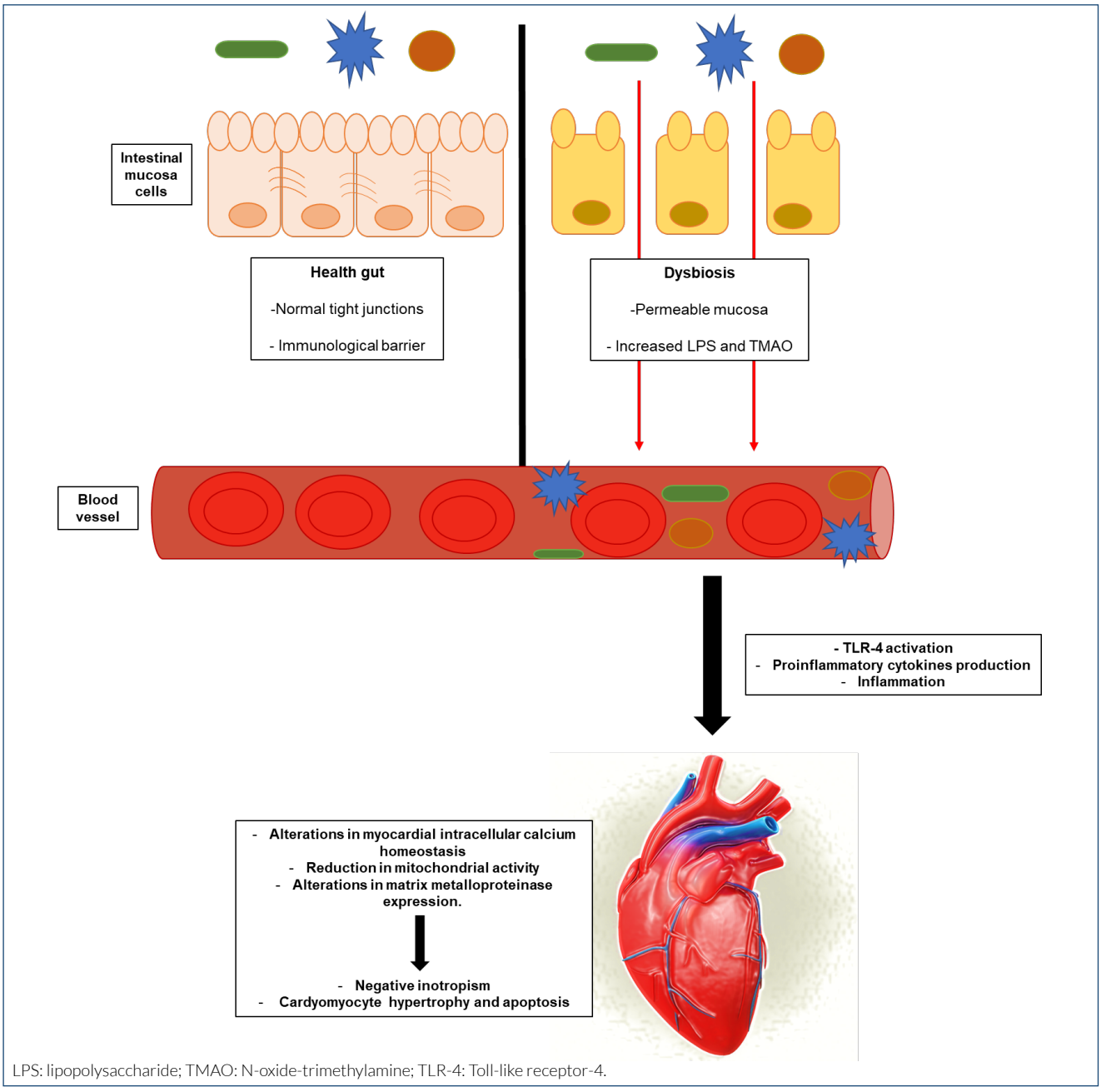

Figure 1. Relationship between gut dysbiosis and heart failure. Under health conditions, gut mucosa has normal tight junctions and works as an immunological barrier. In dysbiosis, mucosa becomes permeable and the levels of lipopolysaccharide and N-oxide-trimethylamine increase. This condition induces an inflammatory response by Toll-like receptor-4 activation, resulting in negative inotropism and cardiomyocyte hypertrophy and apoptosis.

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-documented[26].

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 bacteria[26,27]. Prebiotics are non-digestible carbohydrates used as fermentation substrates and stimulate the proliferation and activity of beneficial intestinal bacteria. It includes oligofructose administered

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].

Antibiotic treatment destroys the balance of intestinal flora, leading to a decrease in flora abundance and changes in composition[27]. A study conducted by Zhou et al. has shown that antibiotics injected to eliminate intestinal bacterial translocation are able to alleviate systemic inflammation and myocardial cell damage in mice with myocardial infarction[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.

FINAL CONSIDERATIONS

Gut dysbiosis can be both a cause and consequence of inflammation in HF and plays a central role in disease pathogenesis and progression. Although some studies have suggested the association among gut dysbiosis, inflammation, and HF, more studies are necessary to elucidate the involved mechanisms. Additionally, the modulation of gut dysbiosis is an important strategy to be tested in clinical studies as a possible intervention to reduce the inflammation and HF severity.

AUTHOR'S CONTRIBUTIONS

FVFF: Conceptualization, Writing – original draft. **ETNM:** Conceptualization, Writing – original draft. **JSS:** Conceptualization, Writing – original draft. **AJTF:** Conceptualization, Writing – original draft **TAV:** Conceptualization, Writing – original draft. **SGZB:** Conceptualization, Writing – original draft. **CRC:** Conceptualization, Writing – original draft.

REFERENCES

1. Albuquerque DC, Souza Neto JD, Bacal F, Rohde LEP, Bernardez-Pereira S, Berwanger O, et al. I registro Brasileiro de insuficiência Cardíaca – Aspectos clínicos, qualidade assistencial e desfechos hospitalares. Arq Bras Cardiol. 2015;104(6):433-42. https://doi.org/10.5935/abc.20150031
2. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL Jr. Inflammation in Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(11):1324-40. https://doi.org/10.1016/j.jacc.2020.01.0143.
3. Yuzefpolskaya M, Bohn B, Nasiri M, Zuver AM, Onat DD, Royzman EA, et al. Gut microbiota, endotoxemia, inflammation, and oxidative stress in patients with heart failure, left ventricular assist device, and transplant. J Hear Lung Transplant. 2020;39(9):880-90. https://doi.org/10.1016/j.healun.2020.02.004
4. Madan S, Mehra MR. Gut dysbiosis and heart failure: navigating the universe within. Eur J Heart Fail. 2020;22(4):1-8. https://doi.org/10.1002/ejhf.1792
5. Schiattarella GG, Sannino A, Esposito G, Perrino C. Diagnostics and therapeutic implications of gut microbiota alterations in cardiometabolic diseases. Trends Cardiovasc Med. 2019;29(3):141-7. https://doi.org/10.1016/j.tcm.2018.08.003
6. Hasan N, Yang H. Factors affecting the composition of the gut microbiota, and its modulation. PeerJ. 2019;7:e7502. https://doi.org/10.7717/peerj.7502
7. Moludi J, Maleki V, Jafari-Vayghyan H, Vaghef-Mehrabany E, Alizadeh M. Metabolic endotoxemia and cardiovascular disease: a systematic review about potential roles of prebiotics and probiotics. Clin Exp Pharmacol Physiol. 2020;47(6):927-39. https://doi.org/10.1111/1440-1681.13250
8. Novakovic M, Rout A, Kingsley T, Kirchoff R, Singh A, Verma V, et al. Role of gut microbiota in cardiovascular diseases. World J Cardiol. 2020;12(4):110-22. https://doi.org/10.4330/wjc.v12.i4.110
9. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med. 1990;323(4):236-41. https://doi.org/10.1056/NEJM199007263230405
10. Sandek A, Anker SD, von Haehling S. The gut and intestinal bacteria in chronic heart failure. Curr Drug Metab. 2009;10(1):22-8. https://doi.org/10.2174/138920009787048374
11. Van Linthout S, Tschöpe C. Inflammation – cause or consequence of heart failure or both? Curr Heart Fail Rep. 2017;14(4):251-65. https://doi.org/10.1007/s11897-017-0337-9
12. Madan S, Mehra MR. Gut dysbiosis and heart failure: navigating the universe within. Eur J Heart Fail. 2020;22(4):629-37. https://doi.org/10.1002/ejhf.1792
13. Alves PHR, Ferron AJT, Costa MR, Hasimoto FK, Gregolin CS, Garcia JL, et al. Relationship between Innate Immune Response Toll-Like Receptor 4 (TLR-4) and the Pathophysiological Process of Obesity Cardiomyopathy. Arq Bras Cardiol. 2021;117(1):91-9. https://doi.org/10.36660/abc.20190788
14. Bowman JD, Surani S, Horseman MA. Endotoxin, Toll-like Receptor-4, and Atherosclerotic Heart Disease. Curr Cardiol Rev. 2017;13(2):86-93. https://doi.org/10.2174/1573403X12666160901145313
15. Sanchez-Rodriguez E, Egea-Zorrilla A, Plaza-Díaz J, Aragón-Vela J, Muñoz-Quezada S, Tercedor-Sánchez L, et al. The gut microbiota and its implication in the development of atherosclerosis and related cardiovascular diseases. Nutrients. 2020;12(3):1-24. https://doi.org/10.3390/nu12030605
16. Tang WHW, Kitai T, Hazen SL, Clinic C, Clinic C, Clinic C. Gut microbiota in cardiovascular health and disease. Circ Res. 2017;120(7):1183-96. https://doi.org/10.1161/CIRCRESAHA.117.309715
17. Hairrman RS, Gouveia CG, Sichinel ÂH, Silva LSA, Oliveira TSS, Farias MN, et al. Tmao and the relationship with cardiovascular disease: the elderly and their physiological aspects. Brazilian J Dev. 2021;7(1):6971-82. https://doi.org/10.34117/bjdv7n1-472
18. Tang WH, Hazen SL. Microbiome, trimethylamine N-oxide, and cardiometabolic disease. Transl Res. 2017;179:108-15. https://doi.org/10.1016/j.trsl.2016.07.007

19. Ufnal M, Pham K. The gut-blood barrier permeability – a new marker in cardiovascular and metabolic diseases? Med Hypotheses. 2017;98:35-7. http://doi.org/10.1016/j.mehy.2016.11.012
20. Carpes LS, Nicoletto BB, Canani LH, Rheinhemer J, Crispim D, Souza GC. Could serum zonulin be an intestinal permeability marker in diabetes kidney disease? PLoS One. 2021;16(6):e0253501. http://doi.org/10.1371/journal.pone.0253501
21. Carrera-Bastos P, Picazo Óscar, Fontes-Villalba M, Pareja-Galeano H, Lindeberg S, Martínez-Selles M, et al. Serum Zonulin and endotoxin levels in exceptional longevity versus precocious myocardial infarction. Aging Dis. 2018;9(2):317-21. http://doi.org/10.14336/AD.2017.0630
22. Silva YP, Bernardi A, Frozza RL. The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. Front Endocrinol (Lausanne). 2020;11:25. http://doi.org/10.3389/fendo.2020.00025
23. Cuesta-Zuluaga J, Mueller NT, Álvarez-Quintero R, Velásquez-Mejía EP, Sierra JA, Corrales-Agudelo V, et al. Higher fecal short-chain fatty acid levels are associated with gut microbiome dysbiosis, obesity, hypertension and cardiometabolic disease risk factors. Nutrients. 2018;11(1):51. http://doi.org/10.3390/nu11010051
24. Yamashita T, Yoshida N, Emoto T, Saito Y, Hirata KI. Two gut microbiota-derived toxins are closely associated with cardiovascular diseases: a review. Toxins (Basel). 20212;13(5):297. http://doi.org/10.3390/toxins13050297
25. Salguero MV, Al-Obaide MAI, Singh R, Siepmann T, Vasylyeva TL. Dysbiosis of Gram-negative gut microbiota and the associated serum lipopolysaccharide exacerbates inflammation in type 2 diabetic patients with chronic kidney disease. Exp Ther Med. 2019;18(5):3461-9. http://doi.org/10.3892/etm.2019.7943
26. Kitai T, Kirsop J, Tang WH. Exploring the Microbiome in Heart Failure. Curr Heart Fail Rep. 2016;13(2):103-9. http://doi.org/10.1007/s11897-016-0285-9
27. Jia Q, Li H, Zhou H, Zhang X, Zhang A, Xie Y, et al. Role and effective therapeutic target of gut microbiota in heart failure. Cardiovasc Ther. 2019;2019:5164298. http://doi.org/10.1155/2019/5164298
28. Davani-Davari D, Negahdaripour M, Karimzadeh I, Seifan M, Mohkam M, Masoumi SJ, et al. Prebiotics: Definition, types, sources, mechanisms, and clinical applications. Foods. 2019;8(3):92. http://doi.org/10.3390/foods8030092
29. Zhou X, Li J, Guo J, Geng B, Ji W, Zhao Q, et al. Gut-dependent microbial translocation induces inflammation and cardiovascular events after ST-elevation myocardial infarction. Microbiome. 2018;6(1):66. http://doi.org/10.1186/s40168-018-0441-4