Revista Portuguesa de Cardiologia 42 (2023) 553–555

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

Gut microbiota dysbiosis and cardiovascular disease – The chicken and the egg

Disbiose da microbiota intestinal e doenças cardiovasculares – O ovo e a galinha

Flávio Reis[a,b,c]

[a] *University of Coimbra, Faculty of Medicine, Institute of Pharmacology & Experimental Therapeutics & Coimbra Institute for Clinical and Biomedical Research (iCBR), Coimbra, Portugal*
[b] *Center for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, 3004-504 Coimbra, Portugal*
[c] *Clinical Academic Center of Coimbra (CACC), Coimbra, Portugal*

Available online 7 March 2023

The human body can be viewed as a superorganism, or metaorganism, because its gastrointestinal (GI) tract, particularly the large intestine, is colonized by trillions of microorganisms (termed the microbiota) that contain hundreds of times more genes (composing the microbiome) than those present in the human body genome. The composition and activity of this community, which is mainly composed of bacteria, co-develop with the host and are modulated throughout life by genetic and environmental factors, including diet, exercise, and medication.

The intestinal microbiota exert several metabolic effects, called co-metabolism, which include contributing to extraction of energy from dietary constituents and the production of important compounds and nutrients for the host, including vitamins and short-chain fatty acids (SCFAs). In addition, the gut microbiota perform other crucial functions for host homeostasis, including protecting against pathogens, maintaining gut barrier integrity and training the immune system. Disturbances in the composition, diversity or function of this bacterial community cause a condition termed dysbiosis. Although it is difficult to define a truly pathogenic bacterial community, the term dysbiosis has been used to describe impaired gut microbiota composition and/or diversity and richness in the context of a disease state. With the recent striking advances in technologies for the analysis of both genes (particularly metagenomic sequencing) and data, research in this field has intensified and extended to various areas of human health. Dysbiosis of the intestinal microbiota has been associated not only with disorders of the GI tract, but also with extra-intestinal diseases, including cardiovascular, metabolic, renal and infectious disease.[1,2]

Changes in the composition of intestinal microbiota have been described in the context of several types of cardiovascular disease (CVD), characterized by an impaired Firmicutes/Bacteroidetes ratio and/or reduction in the prevalence of butyrate-producing bacteria in patients,[3] including those with heart failure (HF),[4,5] compared to healthy subjects. HF is mainly characterized by impaired

E-mail address: freis@fmed.uc.pt

https://doi.org/10.1016/j.repc.2023.03.004

pump function of the heart muscle that effects several other organs and tissues, including blood vessels, lungs, and intestine. Regarding the gut, impaired cardiac function causes reduced intestinal perfusion, mucosal edema, and changes in local pH, which can alter the composition of the microbiota, as described in previous studies comparing HF with non-HF subjects.[6] It has been suggested that gut microbiota dysbiosis, together with changes in the intestinal barrier, particularly the mucosa layer, can alter its permeability and allow translocation into the circulation of bacterial fragments – such as lipopolysaccharide (LPS), an endotoxin – and products of the bacteria and host co-metabolism of dietary components. LPS targets vascular smooth muscle cells, endothelial cells, platelets, macrophages and other immune cells, promoting vascular damage, platelet aggregation and cytokine production, collectively contributing to a state of inflammation, atherosclerosis and atherothrombosis which is common in HF patients as well as in other CVD.[7] Apart from the endotoxemia hypothesis, other mechanisms have been suggested to explain the link between dysbiosis and CVD, including the production of metabolites with proatherosclerotic and prothrombotic properties, especially trimethylamine N-oxide (TMAO), which will be further discussed below.

The crosstalk between gut microbiota and host in CVD is complex and involves various players and factors, in such a way that it is difficult or almost impossible to determine causal relationships. For example, it is unclear whether the presence of HF per se, rather than the existence of comorbidities, especially coronary artery disease (CAD), is responsible for the changes in gut microbiota composition and/or richness. In order to contribute new data to this topic, Kilic et al., in their article published in this issue of the *Journal*,[8] analyzed gut microbial composition using 16S ribosomal DNA (rDNA) sequencing techniques, in stable systolic HF patients with reduced ejection and CAD, compared to a more homogenous group of patients with CAD but without HF (normal ejection fraction). Determination of microbiota composition was complemented with measurement of systemic inflammatory markers, including tumor necrosis factor-alpha, interleukin 1-beta, endotoxin, C-reactive protein, galectin-3, interleukin-6, and lipopolysaccharide-binding protein. The authors found no changes in gut microbial richness and diversity in stable HF patients with CAD compared with those with CAD but without HF, suggesting that stable HF per se may not affect the gut microbial composition. In addition, no statistically significant relationship was observed between inflammatory marker levels and microbial richness and diversity when analyzed at the phylum level.

In their paper, the authors acknowledge some limitations that may bias their results, including the small sample size (40 patients, 19 with HF and CAD and 21 with CAD without HF), the predominance of males, the broad age range (between 40 and 74 years), and the lack of objective questionnaires to report dietary habits. All these pitfalls could indeed affect the ability to obtain robust differences between the groups. In addition, the authors recognize that a patient group with acute decompensated HF could have improved the study. Apart from the limitations due to the difficulty in controlling for factors such as diet and exercise habits, I do feel that the study is also harmed by the background CAD in all the patients. As mentioned above, gut microbiota dysbiosis has been reported in several studies of CVD patients. Kilic et al. were unable to establish a relationship between microbial diversity in the gut and inflammatory markers.[8] However, apart from inflammation, it is nowadays clear that host-microbiota interaction involves several other pathways and players, such as SCFAs and metabolites of bile acids and amino acids (e.g. tryptophan). One of the most studied is TMAO, a metabolite generated by a metaorganismal pathway involving certain bacteria and the host liver. Several experimental studies have shown that TMAO can contribute to atherosclerosis and to metabolic and renal damage by several mechanisms[9]; in addition, clinical studies have suggested that TMAO could be a biomarker of CVD risk, as well as a prognostic marker in HF patients.[10] The study by Kilic et al. would therefore have benefited from the inclusion of measurements of TMAO and other microbial metabolites, as well as from the assessment of SCFAs.

One of the most critical aspects of current knowledge regarding the actual importance of alterations in gut microbiota composition and function in diseases of different types, including CVD, is the difficulty in establishing causality. Is dysbiosis a cause or a consequence of CV disease? Which is the chicken and which is the egg? In order to clarify this and other open questions, studies need better samples and more robust data. Despite the significant advances seen in recent decades, there is still a long way to go in terms of scientific knowledge. Some of the most important tasks to take into account include: (i) unveiling the standard profile – if one actually exists – of dysbiotic intestinal microbiota in terms of CVD; (ii) proving a causal association between dysbiosis and these diseases; (iii) exploring the importance of the interactions between microbiota, immune system and diet for the diseases in question; (iv) standardizing the parameters analyzed in clinical studies used to assess the effects of strategies aimed at modulating the intestinal microbiota; (v) understanding the impact of interventions using more targeted tools, including bacteria produced by bioengineering and bacteriophages; and (vi) developing more comprehensive and consistent studies, which include these more targeted approaches, possibly from a perspective of personalized medicine.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Fernandes R, Viana SD, Nunes S, et al. Diabetic gut microbiota dysbiosis as an inflammaging and immunosenescence condition that fosters progression of retinopathy and nephropathy. Biochim Biophys Acta Mol Basis Dis. 2019;1865:1876–97.
2. Ferreira C, Viana SD, Reis F. Is gut microbiota dysbiosis a predictor of increased susceptibility to poor outcome of COVID-19 patients? An update. Microorganisms. 2020;9:53.
3. Aron-Wisnewsky J, Clément K. The gut microbiome, diet, and links to cardiometabolic and chronic disorders. Nat Rev Nephrol. 2016;12:169–81.
4. Branchereau M, Burcelin R, Heymes C. The gut microbiome and heart failure: a better gut for a better heart. Rev Endocr Metab Disord. 2019;20:407–14.

5. Mamic P, Chaikijurajai T, Tang WHW. Gut microbiome – a potential mediator of pathogenesis in heart failure and its comorbidities: state-of-the-art review. J Mol Cell Cardiol. 2021;152:105–17.
6. Sandek A, Bauditz J, Swidsinski A, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol. 2007;50:1561–9.
7. Seixas-Cambão M, Leite-Moreira AF. Pathophysiology of chronic heart failure. Rev Port Cardiol. 2009;28:439–71 [PMID: 19634500].
8. Kilic O, Ibrahim H, Secme M, et al. The effect of heart failure on gut miocrobial richness and diversity. Rev Port Cardiol. 2023;42, http://dx.doi.org/10.1016/j.repc.2022.06.016.
9. Koeth R, Wang Z, Levison B, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19:576–85.
10. Zhang Y, Wang Y, Ke B, et al. TMAO: how gut microbiota contributes to heart failure. Transl Res. 2021;228:109–25.