The Heart-Gut Microbiome Intersection in Heart Failure

Jefferson L. Vieira,[1] Alessandra F.R.R. Sidrim,[1*] Mandeep R. Mehra[2]*

Hospital de Messejana Dr. Carlos Alberto Studart Gomes,[1] Fortaleza, CE – Brazil

Heart and Vascular Center, Brigham and Women's Hospital, Harvard Medical School,[2] Boston, MA – USA

** Jefferson L Vieira and Alessandra F.R.R. Sidrim contributed equally to this work and are co-first authors*

The human body is co-inhabited by over a trillion microorganisms, including > 2000 species of bacteria, archaea, viruses, and single-celled eukaryotes that live symbiotically with their hosts.[1] The gut microbiota is a dynamic and complex ecological community in the gastrointestinal tract, an essentially anaerobic environment with abundant nutrients and ideal conditions for colonization; it acts as a virtual endocrine system that communicates with organs through metabolism-dependent pathways, releasing *de novo* products and transforming external nutrients and host metabolites into hormone-like signals.[2]

In addition to metabolic benefits, the gut microbiota provides essential capacities for regulating the intestinal epithelial barrier, immune homeostasis, optimal immune responses, and protection against pathogen colonization.[3-5] One of the most important roles of gut microbiota is to act in digestion and nutrient absorption, producing short-chain fatty acids that serve as energy substrate for intestinal epithelial cells. After short-chain fatty acids bind to their receptor, the enteroendocrine hormone peptide YY is released, which regulates host appetite and contributes to dietary energy availability.[6] Intestinal flora act to convert various dietary nutrients into trimethylamine, which is rapidly absorbed and oxidized in the liver to produce trimethylamine N-oxide (TMAO).[7] Some foods, like red meat, eggs, and fish, are rich in nutritional precursors that can be converted into trimethylamine through specific microbial enzymes; therefore, a change in microbiota composition can alter circulating TMAO levels.

Evidence indicates that the composition of gut microbiota changes throughout life via potentially modifiable factors, including medication use, diet, lifestyle, and oxidative stress. Such disruption of microbiota homeostasis results in an imbalance in the microbial community and is referred to as dysbiosis. Gut dysbiosis is associated with the pathogenesis and progression of heart failure (HF), has been linked to immune-mediated subtypes of cardiomyopathy, and has been associated with HF-related comorbidities, including atherosclerosis, hypertension, chronic kidney disease, insulin resistance, and cachexia.[4,8-12] Reduced cardiac output and elevated abdominal venous pressure can lead to intestinal hypoperfusion, mucosal ischemia, and gut barrier disruption (Figure 1). Such alterations have led to the gut hypothesis of HF, which posits that these structural changes contribute to increased intestinal permeability and subsequent bacterial translocation, resulting in elevated circulating endotoxins that correlate with HF severity.[13-16] Endotoxins, which are lipopolysaccharides found in the cell wall of Gram-negative bacilli, can induce the production of pro-inflammatory cytokines and impair endothelial function and peripheral blood flow, resulting in decreased ventricular contractility.[17,18] Likewise, endotoxin and inflammatory cytokines can also exacerbate intestinal permeability, promoting a loop of endotoxin translocation, systemic inflammation, and worsening HF.[19] Other potential mechanisms of the gut hypothesis have also been described, such as the upregulation of sodium-hydrogen exchanger 3 through hypoxia and acidosis in enterocytes, which promotes sodium and fluid retention.[20]

Several studies have supported the gut hypothesis of HF by showing different patterns in gut microbial composition and function between healthy individuals and patients with HF.[21-25] In healthy guts, *Firmicutes* (consisting mainly of *Lactobacillus, Bacillus, Clostridium, Enterococcus,* and *Ruminococcus*) and *Bacteroidetes* (consisting of *Bacteroides* and *Prevotella*) contribute to over 90% of the total bacterial species, also called alpha diversity.[26] Conversely, patients with HF have shifts in the alpha diversity, with an increased abundance of *Bacteroidetes* and a lower abundance of *Firmicutes*, resulting in a lower *Firmicutes*/*Bacteroidetes* ratio than healthy individuals.[21,24] Depletion of bacteria with anti-inflammatory properties, particularly *Firmicutes*, are associated with an increase in the number of pathogenic microbes, such as *Shigella*, *Salmonella,* and *Candida*.[4] The incidence of *Clostridium difficile* infection, which typically occurs after the use of antibiotics, is also higher in this population, as are the genera *Ruminococcus, Hungatella,* and *Succiclasticum*.[4,19,24,25] In advanced HF, an increase in *Pseudomonadota* (formerly *Proteobacteria*), has been demonstrated, a phylum that mainly includes pathogenic Gram-negative bacteria, whose abundance is considered a signature of dysbiosis.[21]

Investigations have indicated that not only does alpha diversity decrease with HF progression, but remains low in patients treated with a left ventricular assist device or heart transplantation,[9] a pattern in line with persistently elevated TMAO levels.[27] Studies of immunosuppression in heart transplantation have demonstrated that gut microbial diversity, inflammation, and oxidative stress are associated with tacrolimus dosing requirements early after engraftment,[28]

Keywords

Gastrointestinal Microbiome; Dysbiosis; Heart failure

Mailing Address: Jefferson Luís Vieira •
Hospital de Messejana Dr. Carlos Alberto Studart Gomes, Av. Frei Cirilo, 3480, Postal Code 60840-285, Messejana, Fortaleza, CE – Brazil
E-mail: jefvieira@yahoo.com.br
Manuscript received March 31, 2022, revised manuscript April 13, 2022, accepted Maty 05, 2022

DOI: https://doi.org/10.36660/abchf.20220039

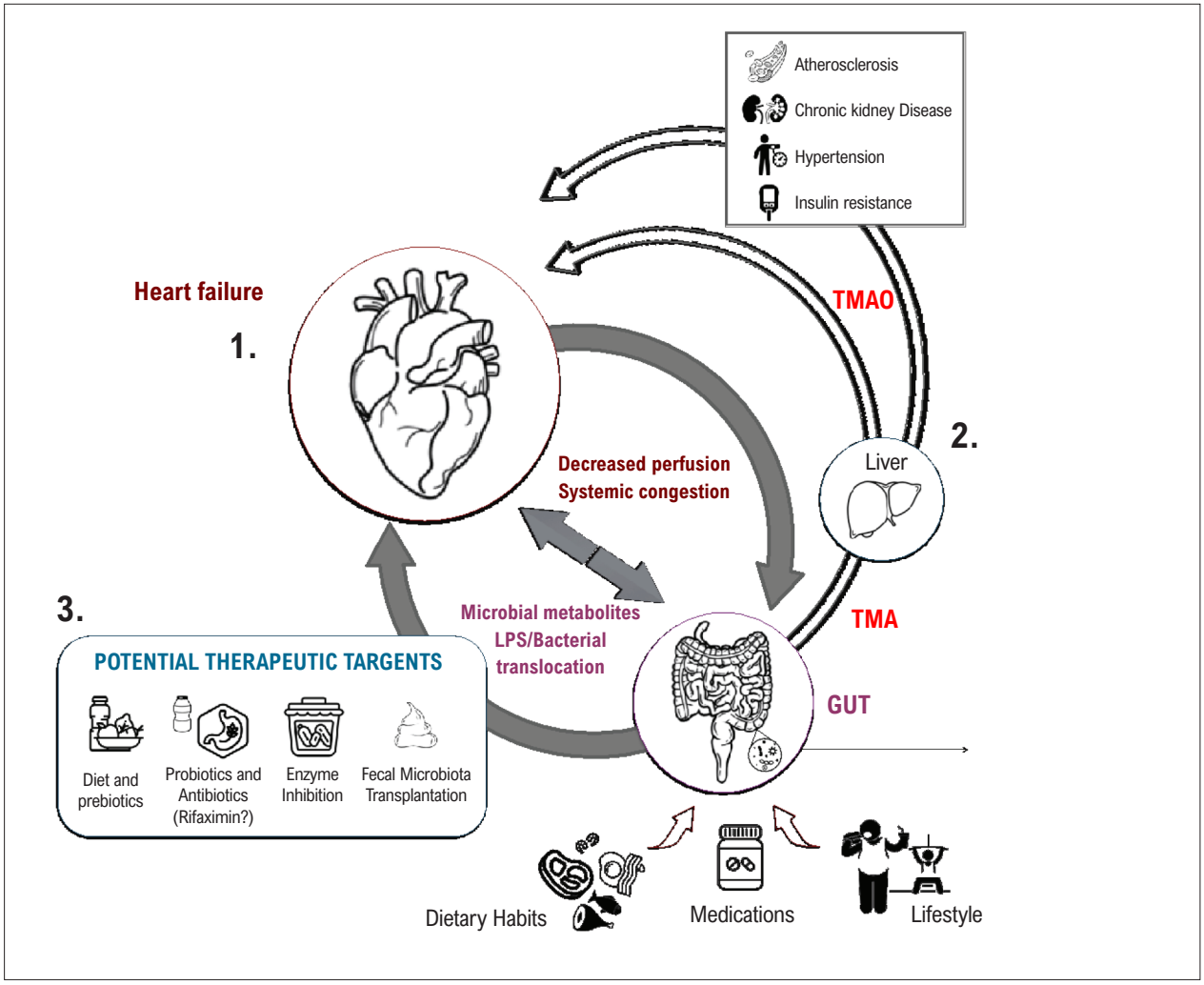

Figure 1 - *1) Reduced cardiac output and elevated abdominal venous pressure can lead to intestinal hypoperfusion, mucosal ischemia, and gut barrier disruption, with subsequent bacterial translocation and increased circulating endotoxins (lipopolysaccharides). Lipopolysaccharides induce the production of pro-inflammatory cytokines, resulting in decreased ventricular contractility. Likewise, endotoxin and inflammatory cytokines can also exacerbate intestinal permeability, promoting a loop of endotoxin translocation, systemic inflammation, and worsening heart failure. 2) Intestinal flora convert various dietary nutrients into trimethylamine, which is converted in the liver to trimethylamine N-oxide. Gut dysbiosis is associated with the pathogenesis and progression of heart failure and heart failure-related comorbidities, including atherosclerosis, hypertension, chronic kidney disease, insulin resistance, and cachexia. 3) Several potential therapeutic approaches have already been proposed, including dietary interventions, prebiotics, probiotics, trimethylamine N-oxide inhibitors, sodium-hydrogen exchanger 3 inhibitors, and fecal microbiota transplantation, as well as intestinal microenvironment modulators (Rifaximin).*

reinforcing the gut hypothesis at all stages of HF, from cardiac injury to end-stage HF and even after advanced therapies. Various HF phenotypes, such as preserved ejection fraction, require further study to understand the relationship between congestion and dysbiosis patterns. Pilot studies have revealed that the microbiota of patients with HF with preserved ejection fraction are imbalanced compared to healthy controls, with more *Enterococcus* and *Lactobacillus* and less *Butyricicoccus, Sutterella, Lachnospira*, and *Ruminiclostridium* at the genus level[29] and a non-significant decrease in the *Firmicutes*/*Bacteroidetes* ratio. How these alterations influence the observed pathobiology remains uncertain.

All of these changes in gut microbiota are linked to different physiological effects, such as cell cycle control, cell division, chromosome partitioning, ion transport, ribosomal structure, and amino acid metabolism. Identifying the composition of gut microbes is complex and requires sophisticated stool sample processing with 16S rRNA gene sequencing and whole metagenomic profiling. However, the use of surrogate circulating metabolites is less complicated and is readily available.[19,25] It has been discovered that certain microbial metabolites have recognized roles in HF pathophysiology, such as short-chain fatty acids, TMAO, amino acid metabolites, and bile acids; they may be promising therapeutic targets for gut dysbiosis in HF.[12] In fact, several therapeutic approaches have already been proposed, including dietary interventions, prebiotics, probiotics, TMAO inhibitors, sodium-hydrogen exchanger

3 inhibitors, and fecal microbiota transplantation, as well as intestinal microenvironment modulators (Rifaximin), but additional studies are still needed.[1] Further exploration of the heart-gut axis in the pathophysiology of HF may lead to advances in innovative individualized risk stratification and therapeutic interventions for patients with HF.

Author Contributions

Conception and design of the research: Vieira JL, Mehra MR; Acquisition of data and Critical revision of the manuscript for intellectual content: Vieira JL, Sidrim AFRR, Mehra MR; Analysis and interpretation of the data: Vieira JL, Sidrim AFRR; Writing of the manuscript: Vieira JL, Sidrim AFRR.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

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

References

1. Gallo A, Macerola N, Favuzzi AMR, Nicolazzi MA, Gasbarrini A, Montalto M. The Gut in Heart Failure: Current Knowledge and Novel Frontiers. Med Princ Pract. 2022. Epub ahead of print. doi: 10.1159/000522284.
2. Garcia-Reyero N. The Clandestine Organs of the Endocrine System. Gen Comp Endocrinol. 2018;257:264-71. doi: 10.1016/j.ygcen.2017.08.017.
3. Pickard JM, Zeng MY, Caruso R, Núñez G. Gut Microbiota: Role in Pathogen Colonization, Immune Responses, and Inflammatory Disease. Immunol Rev. 2017;279(1):70-89. doi: 10.1111/imr.12567.
4. 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. doi: 10.1016/j.yjmcc.2020.12.001.
5. Barbara G, Barbaro MR, Fuschi D, Palombo M, Falangone F, Cremon C, et al. Inflammatory and Microbiota-Related Regulation of the Intestinal Epithelial Barrier. Front Nutr. 2021;8:718356. doi: 10.3389/fnut.2021.718356.
6. Chen X, Li HY, Hu XM, Zhang Y, Zhang SY. Current Understanding of Gut Microbiota Alterations and Related Therapeutic Intervention Strategies in Heart Failure. Chin Med J.2019;132(15):1843-55. doi: 10.1097/CM9.0000000000000330.
7. Farhangi MA. Gut Microbiota-dependent Trimethylamine N-oxide and All-cause Mortality: Findings from an Updated Systematic Review and Meta-analysis. Nutrition. 2020;78:110856. doi: 10.1016/j.nut.2020.110856.
8. Pasini E, Aquilani R, Testa C, Baiardi P, Angioletti S, Boschi F, et al. Pathogenic Gut Flora in Patients with Chronic Heart Failure. JACC Heart Fail. 2016;4(3):220-7. doi: 10.1016/j.jchf.2015.10.009.
9. 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 Heart Lung Transplant. 2020;39(9):880-90. doi: 10.1016/j.healun.2020.02.004.
10. Kitai T, Kirsop J, Tang WH. Exploring the Microbiome in Heart Failure. Curr Heart Fail Rep. 2016;13(2):103-9. doi: 10.1007/s11897-016-0285-9.
11. 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(4):407-14. doi: 10.1007/s11154-019-09519-7.
12. Madan S, Mehra MR. Gut Dysbiosis and Heart Failure: Navigating the Universe Within. Eur J Heart Fail. 04 2020;22(4):629-37. doi:10.1002/ejhf.1792.
13. Nagatomo Y, Tang WH. Intersections Between Microbiome and Heart Failure: Revisiting the Gut Hypothesis. J Card Fail. 2015;21(12):973-80. doi: 10.1016/j.cardfail.2015.09.017.
14. Tang WH, Kitai T, Hazen SL. Gut Microbiota in Cardiovascular Health and Disease. Circ Res. 2017;120(7):1183-96. doi: 10.1161/CIRCRESAHA.117.309715.
15. Tang WH, Hazen SL. The Gut Microbiome and Its Role in Cardiovascular Diseases. Circulation. 2017;135(11):1008-10. doi: 10.1161/CIRCULATIONAHA.116.024251.
16. Harikrishnan S. Diet, the Gut Microbiome and Heart Failure. Card Fail Rev. 2019;5(2):119-122. doi: 10.15420/cfr.2018.39.2.
17. Yang D, Dai X, Xing Y, Tang X, Yang G, Harrison AG, et al. Intrinsic Cardiac Adrenergic Cells Contribute to LPS-induced Myocardial Dysfunction. Commun Biol. 2022;5(1):96. doi: 10.1038/s42003-022-03007-6.
18. Alí A, Boutjdir M, Aromolaran AS. Cardiolipotoxicity, Inflammation, and Arrhythmias: Role for Interleukin-6 Molecular Mechanisms. Front Physiol. 2019;9:1866. doi: 10.3389/fphys.2018.01866.
19. Chaikijurajai T, Tang WHW. Gut Microbiome and Precision Nutrition in Heart Failure: Hype or Hope? Curr Heart Fail Rep. 2021;18(2):23-32. doi: 10.1007/s11897-021-00503-4.
20. Polsinelli VB, Sinha A, Shah SJ. Visceral Congestion in Heart Failure: Right Ventricular Dysfunction, Splanchnic Hemodynamics, and the Intestinal Microenvironment. Curr Heart Fail Rep. 2017;14(6):519-28. doi: 10.1007/s11897-017-0370-8.
21. Sun W, Du D, Fu T, Han Y, Li P, Ju H. Alterations of the Gut Microbiota in Patients With Severe Chronic Heart Failure. Front Microbiol. 2022;12:813289. doi: 10.3389/fmicb.2021.813289.
22. Kamo T, Akazawa H, Suda W, Saga-Kamo A, Shimizu Y, Yagi H, et al. Dysbiosis and Compositional Alterations with Aging in the Gut Microbiota of Patients with Heart Failure. PLoS One. 2017;12(3):e0174099. doi: 10.1371/journal.pone.0174099.
23. Luedde M, Winkler T, Heinsen FA, Rühlemann MC, Spehlmann ME, Bajrovic A, et al. Heart Failure is Associated with Depletion of Core Intestinal Microbiota. ESC Heart Fail. 2017;4(3):282-90. doi: 10.1002/ehf2.12155.
24. Mayerhofer CCK, Kummen M, Holm K, Broch K, Awoyemi A, Vestad B, et al. Low Fibre Intake is Associated with Gut Microbiota Alterations in Chronic Heart Failure. ESC Heart Fail. 2020;7(2):456-66. doi: 10.1002/ehf2.12596.
25. Cui X, Ye L, Li J, Jin L, Wang W, Li S, et al. Metagenomic and Metabolomic Analyses Unveil Dysbiosis of Gut Microbiota in Chronic Heart Failure Patients. Sci Rep. 2018;8(1):635. doi: 10.1038/s41598-017-18756-2.

26. Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. Microorganisms. 2019;7(1):14. doi: 10.3390/microorganisms7010014.

27. Yuzefpolskaya M, Bohn B, Javaid A, Mondellini GM, Braghieri L, Pinsino A, et al. Levels of Trimethylamine N-Oxide Remain Elevated Long Term After Left Ventricular Assist Device and Heart Transplantation and Are Independent From Measures of Inflammation and Gut Dysbiosis. Circ Heart Fail. 2021;14(6):e007909. doi: 10.1161/CIRCHEARTFAILURE.120.007909.

28. Jennings DL, Bohn B, Zuver A, Onat D, Gaine M, Royzman E, et al. Gut Microbial Diversity, Inflammation, and Oxidative Stress are Associated with Tacrolimus Dosing Requirements Early After Heart Transplantation. PLoS One. 2020;15(5):e0233646. doi: 10.1371/journal.pone.0233646.

29. Huang Z, Mei X, Jiang Y, Chen T, Zhou Y. Gut Microbiota in Heart Failure Patients With Preserved Ejection Fraction (GUMPTION Study). Front Cardiovasc Med. 2022;8:803744. doi: 10.3389/fcvm.2021.803744.