



Modulating gut microbial metabolism in heart failure: Opportunities and challenges



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Alterations in gut microbial composition and metabolism have been mechanistically linked to the development of heart failure (HF) [1]. However, the promise of targeting the gut microbiome to prevent or even reverse disease progression remains somewhat unfulfilled despite the exponential growth of technological advances that have allowed us to gain insights and deliver therapeutic interventions to modulate gut microbial metabolism [2]. In a recent issue of *EBioMedicine*, an esteemed group of clinical investigators from Norway and Brazil reported their primary findings of the GutHeart trial, a prospective multicenter study that demonstrated that short-term treatment of either rifaximin or *Saccharomyces boulardii* did not improve cardiac function in patients with HF with reduced ejection fraction [3]. Secondary endpoints, such as cardiac and inflammatory biomarkers or gut microbial metabolites (e.g. trimethylamine N-oxide [TMAO]), were also unaffected by either intervention, even though rifaximin did alter gut microbial composition as expected. These findings were in stark contrast with prior observations that *Saccharomyces boulardii* may reestablish the production of short-chain fatty acids (SCFA) and improve cardiac function [4]. Assuming that the gut microbiome remains a therapeutic target for HF, findings from the GutHeart study highlight several key opportunities and challenges in the pursuit of precision medicine as clinical investigations continue in this area.

First, we need to identify the right patients for the interventions. As the authors alluded to in their paper, the fact that their study cohort was relatively compensated and with minimal dysbiosis may have limited the effectiveness of the utilized interventions. Future investigations will depend on the ability to identify vulnerable

populations, perhaps through the use of specific biomarkers, that may better benefit from these interventions. In searching for a useful biomarker, there is debate on whether or not to utilize stool microbial composition as a marker of dysbiosis, since stool metagenomics may not reflect the true intestinal microbial content, and microbial-mediated metabolites can be affected by absorption and clearance mechanisms of the human host and can be heavily influenced by dietary intake and behavioral factors [5]. Therefore, finding a reliable biomarker to identify the appropriate vulnerable patient population for intervention remains a top priority.

Second, we need to identify the right interventions to target the pathophysiologic mechanisms of interest. While the beneficial effects of probiotics, including altering intestinal pH, competing against pathogenic organisms, and modifying host immune responses, are touted as a global panacea for dysbiosis, accumulating evidence supports the notion that the efficacy of probiotics is likely both strain-specific and disease-specific. Furthermore, acute or periodic ingestion of a few microbial species may not produce the necessary effects to shift an entire microbial community residing in an intact gut environment. Although previous animal models of HF have demonstrated some beneficial effects of probiotic administration in acute ischemic models [6], high-quality prospective human studies are still lacking. Indeed, there was limited evidence to show that *Saccharomyces boulardii* in the GutHeart study had any impact on local or systemic SCFA levels. On the other hand, rifaximin is commonly used for the treatment of irritable bowel disease and bacterial overgrowth, but its role in modulating gut microbial composition is still evolving. In prior non-cardiac studies, rifaximin did not alter the levels of cardiovascularly important microbial metabolites TMAO or SCFA, but did modulate gut microbial compositions [7-9]. These observations are largely consistent with the neutral findings from GutHeart, and may imply that better understanding of the targeted mechanisms may be necessary prior to the conduct of human intervention studies. It is also important to recognize that even if initial (short-term) effects can lead to a desirable alteration in gut microbiota-dependent metabolites and a beneficial effect, long-term antibiotic treatment can ultimately lead to potential harm if antibiotic-resistant microbes with survival benefits adversely dominate the intestinal biome. Therefore, we must understand how to appropriately balance the gut ecosystem as we deliver the interventions.

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Third, we need to identify the best timing for the intervention. Short term changes in gut microbial composition and function following dietary interventions have previously been shown to occur within days to weeks [10]. Nevertheless, while it's possible that the neutral results reported in the GutHeart study represent a lack of any changes, it's also possible that short-term changes did occur but were overcome by other host factors (such as changes in clinical status) or environmental factors (such as changes in dietary habits) over time. Furthermore, the assumption that modulating dysbiosis can alter the natural history of HF remains largely untested, as upstream dietary interventions that prevent HF may provide a greater impact than any intervention after HF ensues. In this line of thought, the consistency, reproducibility, and clinical relevance of the endpoints of interest from dietary or metabolic modulation still needs further definition in the HF population.

The neutral findings in some ways are a reminder that extrapolation of interventions that have theoretic effects on the gut microbiome for other indications needs to be confirmed with rigorous investigations in HF such as the GutHeart trial. There is the much-needed work ahead in seeking a deeper understanding of the unique therapeutic mechanisms targeting the gut microbiome that may alter the natural history of HF.

Declaration of Competing Interest

Dr. Chaikijurajai has no relationships to disclose. Dr. Tang is a consultant for Sequana Medical A.G., Owkin Inc, Relypsa Inc, preCARDIA Inc, Cardiol Therapeutics Inc, Genomics plc, and has received honorarium from Springer Nature for authorship/editorship and American Board of Internal Medicine for exam writing committee participation - all unrelated to the subject and contents of this paper.

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References

- [1] Tang WHW, Li DY, Hazen SL. Dietary metabolism, the gut microbiome, and heart failure. *Nat Rev Cardiol* 2019;16:137–54.
- [2] 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.
- [3] Awoyemi A, Mayerhofer C, Felix AS, Hov JR, Moscovitch SD, Lappegard KT, Hovland A, Halvorsen S, Halvorsen B, Gregersen I, Svardal A, Berge RK, Hansen SH, Gotz A, Holm K, Aukrust P, Akra S, Seljeflot I, Solheim S, Lorenzo A, Gullestad L, Troseid M, Broch K. Rifaximin or Saccharomyces boulardii in heart failure with reduced ejection fraction: results from the randomized GutHeart trial. *EBioMedicine* 2021;70:103511.
- [4] Costanza AC, Moscovitch SD, Faria Neto HC, Mesquita ET. Probiotic therapy with Saccharomyces boulardii for heart failure patients: a randomized, double-blind, placebo-controlled pilot trial. *Int J Cardiol* 2015;179:348–50.
- [5] Chaikijurajai T, Tang WHW. Gut microbiome and precision nutrition in heart failure: hype or hope? *Curr Heart Fail Rep* 2021;18:23–32.
- [6] Gan XT, Ettinger G, Huang CX, Burton JP, Haist JV, Rajapurohitam V, Sidaway JE, Martin G, Gloor GB, Swann JR, Reid G and Karmazyn M. Probiotic administration attenuates myocardial hypertrophy and heart failure after myocardial infarction in the rat. *Circ Heart Fail* 2014;7:491–9.
- [7] Acosta A, Camilleri M, Shin A, Linker Nord S, O'Neill J, Gray AV, Lueke AJ, Donato LJ, Burton DD, Szarka LA, Zinsmeister AR, Golden PL, Fodor A. Effects of rifaximin on transit, permeability, fecal microbiome, and organic acid excretion in irritable bowel syndrome. *Clin Transl Gastroenterol* 2016;7:e173.
- [8] Kimber C, Zhang S, Johnson C, West 3rd RE, Prokopenko AJ, Mahnken JD, Yu AS, Hoofnagle AN, Ir D, Robertson CE, Miyazaki M, Chonchol M, Jovanovich A, Kestenbaum B, Frank DN, Nolin TD, Stubbs JR. Randomized, placebo-controlled trial of rifaximin therapy for lowering gut-derived cardiovascular toxins and inflammation in CKD. *Kidney360*. 2020;1:1206–16.
- [9] Macpherson ME, Hov JR, Ueland T, Dahl TB, Kummen M, Otterdal K, Holm K, Berge RK, Mollnes TE, Troseid M, Halvorsen B, Aukrust P, Fevang B, Jorgensen SF. Gut microbiota-dependent trimethylamine N-oxide associates with inflammation in common variable immunodeficiency. *Front Immunol* 2020;11:574500.
- [10] David LA, Materna AC, Friedman J, Campos-Baptista MI, Blackburn MC, Perrotta A, Erdman SE, Alm EJ. Host lifestyle affects human microbiota on daily timescales. *Genome Biol* 2014;15:R89.