Editorial

Following the Scent of Microbes Within: The Heart-Gut Connection

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Metabolomics is the study of small organic molecules in biochemical pathways, some of which have been implicated in heart failure pathogenesis and progression. In heart failure, metabolomic analyses have ranged from identifying novel metabolic biomarkers to exploring the exhaled metabolome.[1,2] However, there are major challenges to overcome, given the vast number of metabolites generated from these analyses that may lack specificity and mechanistic insights into their potential contributory roles in disease pathogenesis.[3]

Applications of metabolomics to the evaluation of the gut microbiome have yielded some intriguing insights into cross-talks between the heart and other key organs, especially the intestines, kidneys, and lungs. For example, alterations in the diversity and composition of the intestinal microbiome have been associated with the pathogenesis of heart failure.[4] Observational studies have demonstrated that heart failure patients have higher concentrations of adherent bacteria in the gut mucus during sigmoidoscopy and in fecal contents.[5,6] Dietary metabolites from intestinal microbiome such as short-chain fatty acids and trimethylamine *N*-oxide have been implicated in detailed mechanistic explorations in the setting of atherosclerotic heart disease and heart failure.[7] Furthermore, dietary and pharmacologic interventions that track with changes in metabolite levels have shown promising therapeutic potential.[7,8]

Small intestinal bacterial overgrowth (SIBO) is an established gastrointestinal diagnosis that is associated with alterations in gastrointestinal structure, acidity, mucosa, and/or peristaltic activity.[9] Recent investigations have begun to tease out some unexpected interactions between intestinal microbes and cardiovascular diseases. For example, a retrospective study reviewing glucose hydrogen/methane breath tests revealed an intriguing association between SIBO presence and disease burden of coronary artery disease independently from traditional cardiovascular risk factors.[10] In patients with heart failure, a distinct exhaled metabolome can be identified, and exhaled acetone or pentane has tracked with adverse outcomes.[2,11,12] Bacterial fermentation of nonabsorbed carbohydrates is assumed to be the sole source of hydrogen and methane. However, the measurement of these exhaled compounds can also be influenced by a variety of host, technique, or assay variables, which may explain its wide range of diagnostic sensitivity (17%−68%) and specificity (44%−86%) for SIBO.[13]

It is in this context that the provocative study by Mollar et al in this issue of the *Journal of Cardiac Failure* has implicated a potential link between heart failure disease progression and small bowel bacterial overgrowth.[14] This study of 102 patients with heart failure used a noninvasive method of lactulose breath test with measurement of lactulose-induced exhaled hydrogen and methane to assess for SIBO. Area under the curve for exhaled hydrogen (AUC-H_2), but not exhaled methane, was associated with all-cause mortality and hospitalization.[14] In addition, the traditional cutoff of baseline or peak hydrogen and methane levels for diagnosis of SIBO did not provide prognostic value for death or heart failure admission (only for death or any admission). Thus, the specificity of this observation to heart failure syndrome remains unclear. Moreover, at baseline, those with higher AUC-H_2 had more heart failure hospitalizations within the previous 30 days, as well as more renal insufficiency and higher natriuretic peptide levels (albeit not statistically significant for the latter).[14] Addition of AUC-H_2 to the base model improved the c-statistic, but not significantly so, and the overall model c-statistic was modest (0.67).[14] There was also substantial overlap across measurements between those with and without events (as shown in the supplemental materials), which may challenge the ultimate clinical utility of AUC-H_2 in patients with heart failure.

Although this study does not directly establish a causal relationship between SIBO and heart failure pathogenesis,

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it does raise a few putative mechanistic insights into heart failure pathophysiology that should be further explored. From this study we have a very limited characterization of the degree of right heart failure in the study population (notably with mean left ventricular ejection fraction of 45%, median N-terminal pro−B-type natriuretic peptide levels of 3,276 pg/mL, and mean urea of 72 mg/dL). We also have limited information on their gastrointestinal signs and symptoms. Splanchnic venous congestion, a known risk factor for disease progression often associated with right heart failure, may lead to increased permeability of the gut barrier and transient translocation of bacterial endotoxins or low-grade bacteremia which may promote heart failure progression. In addition, inflammatory interactions with bacterial overgrowth may be contributing, as suggested by higher trending TNF-α levels with AUC-H_2 quartiles and in previous studies.[14,15] Meanwhile, the prognostic implications of hydrogen-producing (but not methane-producing) microbes is also unclear.

The importance of recognizing the contributory role of intestinal bacteria in patients with heart failure largely depends on its therapeutic implications. At present, it is unclear whether heart failure optimization with guideline-directed medical therapies results in favorable alterations in gut acidity and peristalsis that may attenuate the predisposition to intestinal bacterial overload. There may also be implications in the use of proton-pump inhibitors in heart failure patients, which have a modest impact on increasing risk of SIBO.[16] Future studies should assess the response in bacterial overgrowth to the treatment of heart failure. Conversely, a causative mechanism could be surmised if treatment of small bowel bacterial overgrowth with antimicrobials such as rifaximin alters the prognosis of concurrent heart failure. However, until there is better understanding of the intricate interactions between intestinal bacteria and the heart failure syndrome, we caution against the oversimplification of this heart-gut link, and advocate looking for more answers by following the scent of the microbes within.

Disclosures

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