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Dietary Metabolism, Gut Microbiota and Acute Heart Failure

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The human gut harbors trillions of microbial organisms. The overall architecture of the microbial community is remarkably stable over time within an individual and their family members. However, gut microbial composition and function are also profoundly influenced by dietary exposure and the local intestinal environment. Thus, the combined functions of the gut microbiome and host genotype together determine global physiological responses to varied nutrient inputs, with both dynamic and adaptive functional components from gut microbiome and host participating. And the gut microbiome has been increasingly been appreciated to play important physiologic and metabolic roles in our overall health and disease.

It has long been recognized that heart failure (HF) is associated with altered intestinal function, likely as a consequence of ischemia and/or congestion within the intestines. There is enhanced gut bacterial translocation due to impaired intestinal barrier function, as well as release and detection of heightened levels of endotoxin-like compounds within the circulation, accompanied by heightened inflammatory responses and increased indices of oxidative stress. On the other hand, metabolic derangements as a result of altered gut microbial metabolism may also influence the overall host metabolic processes. Our group has discovered that gut microbiota, via specific microbial choline trimethylamine lyases, play an obligatory role in the generation of trimethylamine *N*-oxide (TMAO), a bioactive metabolite of choline or *L*-carnitine that contributes to cardiovascular disease pathogenesis. [1, 2] In recent studies, we further observed that patients with HF have significantly higher levels of TMAO compared to age- and sex-matched non-HF subjects.[3] We further showed that elevated plasma TMAO portends poorer long-term survival, even after adjusting for cardio-renal parameters, and regardless of underlying etiology.[3] Moreover, our preliminary animal HF model studies also demonstrated a direct mechanistic link between increased dietary choline or TMAO intake, circulating TMAO levels, and adverse ventricular remodeling.[4]

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In this issue of *Heart*, Suzuki and colleagues extend these observations by describing a cohort of patients admitted for acute decompensated HF in which TMAO levels were drawn within 24 hours of admission. They observed that elevated levels of TMAO (in the ranges similar to the highest quartiles of the high risk cohorts in the original human studies)[3] identified a subset of patients with more advanced clinical profile and at greater risk of in-hospital death, as well as either all-cause mortality, or the composite of death/heart failure at one year.[5] TMAO is renally cleared, and accordingly, renal dysfunction (blood urea nitrogen and estimated glomerular filtration rate) appears to be a strong determinant of TMAO levels. Nevertheless, the in-hospital death prediction was particularly strong and independent of several common prognostic factors such as ADHERE risk score (systolic blood pressure, blood urea nitrogen and creatinine) and natriuretic peptide levels. Indeed, congestion itself has been shown in multiple studies to alter the intestinal barrier and potentially facilitate bacterial translocation, yet there are limited insights into the metabolic derangements with potential for causal impact on adverse myocardial remodeling and HF progression, such as TMAO,[3, 4] that can be generated from host-microbial interactions in acute HF. It is interesting to note that bedside assessment of congestion (elevated jugular venous distention, pulmonary edema, orthopnea) were not independently associated with elevated TMAO levels. These findings also suggest that understanding why TMAO levels are elevated in the setting of HF may provide important insights into how gut microbiota may contribute to disease progression in HF.

The competing risks between measurements of TMAO and renal function have been well-documented in previous studies, yet the prognostic value of TMAO remained robust at least for in-hospital mortality. It is not uncommon to witness many of these parameters (blood urea nitrogen, creatinine) are increased at the time of admission or following aggressive diuretic therapy, and clearly TMAO may serve as an important uremic toxin. However, the precise underlying reason(s) leading to increased TMAO levels cannot be reliably determined from this post-hoc cohort study simply by associating plasma levels with outcomes because it does not take into account interim treatment and responses. In addition, whether TMAO levels track with clinical stability is unknown. Dynamic changes of TMAO levels - such as the changes in TMAO level as patients transition from compensated to decompensated state, the time course for such change, and whether they return to chronic stable levels following stabilization - will be key questions to be answered.

What are the key clinical implications of these findings? If elevated TMAO levels are simply indicative of accumulation of uremic toxins due to impaired end-organ (kidney, intestinal) function or perfusion in the acute setting, more aggressive strategies to improve circulatory support, the current primary therapeutic strategy, seems reasonable. However, the ability of TMAO levels to predict adverse prognostic outcomes independent of cardiorenal indices suggests a potential contributory role for TMAO in adverse ventricular remodeling and heart failure development. Consistent with this, recent animal model studies show high TMAO, whether through dietary choline, or TMAO directly, markedly enhanced adverse ventricular remodeling, including myocardial fibrosis, functional impairment, and pulmonary edema. Thus, the results of Suzuki and colleagues,[5] coupled with other recent studies,[6] suggest that strategies to reduce TMAO levels may provide incremental therapeutic benefit. Indeed, in recent studies we showed that inhibition in TMAO levels with a non-lethal microbial

enzyme inhibitor attenuated diet induced atherosclerosis.[6] Whether similar approaches provide benefit in the setting of heart failure remain to be determined. Moreover, alternative approaches at TMAO reduction should be considered, such as modulating dietary protein intake by reducing the proportion of TMAO rich precursor nutrients. It is of interest that few studies have definitively linked dietary associations with HF outcome in either acute or chronic HF settings, and thus there are currently no dietary guideline recommendations for managing HF patients. The truth is, there has been very limited understanding on how dietary modulations should be considered in the acute HF setting. Regarding long-term effects, there are promising new findings of the potential benefits of the Mediterranean Diet in lowering the risk of developing HF,[7] an intervention that has much promise in altering the circulating TMAO levels in other studies.[8] Further studies are warranted to determine if circulating TMAO levels can serve as a guidance to tailor dietary modulation or therapeutic interdiction in either acute or chronic HF. It would be impactful if treatment strategy guided by elevated TMAO levels can alter the natural history of this otherwise morbid and costly clinical condition.

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