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Gut microbiota involvement in ventricular remodeling post myocardial infarction: New insights into how to heal a broken heart

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It is now well recognized that gut microbiota play a vital role in maintenance of health and disease susceptibility. The number of bacterial genes encoded within the human gut vastly outnumber the total complement of genes in *Homo sapiens*, endowing the gut microbiome with enormous potential for production of a range of functionally active metabolites. Indeed, gut microbiota function as an endocrine organ, converting environment-driven nutritional cues into hormone-like signals that can impact host metabolic phenotypes[1]. The mechanisms linking gut microbiota to cardiovascular disease (CVD) are multifaceted, and include direct effects of microbial metabolites on atherosclerosis and thrombosis development, as well as immune modulation by bacteria and their products. The case of trimethylamine N-oxide (TMAO)[2,3], a microbiota-dependent metabolite derived from nutrients abundant in a Western diet, represents the first of now a multitude of bacterial products with evidence for a contributory role in CVD. For example, short-chain fatty acids (SCFAs) produced during microbial fermentation of complex carbohydrates, possess immunomodulatory properties that may impact CVD risk[1].

Due to recent connections drawn between microbial metabolism and CVD, the gut microbiome has emerged as an intriguing target for prevention and treatment of a variety of cardiometabolic conditions. Modulation of gut microbiota with probiotics, diet, or non-lethal microbial enzyme inhibitors, are all areas of active research in heart failure (HF)[1]. Early studies by Lam et al were among the first to highlight the potential for microbes to impact ventricular remodelling following myocardial infarction (MI)[4]. In that study, both oral administration of the antibiotic vancomycin or the probiotic Goodbelly (containing

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Lactobacillus plantarum 299v and *Bifidobacterium lactis* Bi-07) prior to ischemia-reperfusion (I/R) injury significantly reduced infarct size and improved myocardial function in rats. A separate study by Gam et al expanded on these findings with pre-administration of the probiotic *Lactobacillus rhamnosus* GR-1, this time using a chronic coronary artery ligation model, and reported preservation of ventricular function[5]. Human studies with probiotics for HF remain in their infancy. However, some intriguing results were recently reported in one small double-blind, placebo-controlled study with *Saccharomyces boulardii*[6]. Stable HF subjects were randomized to placebo vs probiotic treatment for 3 months, with significant improvement in both ejection fraction and left atrial diameter reported in the probiotic group[6]. While the clinical trial was small, these studies highlight the potential of probiotics as a possible therapy for HF. Mechanisms involved in the observed beneficial effects with probiotics on the whole are unknown, but may include changes in inflammation, gut leakiness and leptin.

In this issue of *Circulation*, Dr. Hsieh and colleagues add to the growing data linking gut microbiota to myocardial function and repair following MI[7]. Their studies begin with the remarkable observation that gut microbiota suppression with an oral cocktail of poorly absorbed antibiotics markedly enhanced the rates of post MI ventricular rupture and death in a murine model of chronic left anterior descending artery ligation. Importantly, they also showed that “microbial reconstitution” with fecal transplantation from untreated donors prior to MI significantly improved survival, suggesting gut microbiota involvement in early myocardial repair. New mechanistic insight surrounding the impact of gut microbiota on ventricular remodelling is provided via a series of add-back experiments, which suggest the salutary effects in the post MI setting may be mediated in part by gut microbiota-generated SCFAs, which induced recruitment of myeloid cells to the heart. Either dietary supplementation with SCFAs or i.v. infusion of the monocytic cell line RAW264.7 provided 1d following MI, significantly reversed the adverse effects of antibiotics on mortality and ventricular rupture rates. The authors also demonstrate that a SCFA-producing probiotic mixture (*L. acidophilus, B. bifidum, L. casei, L. paracasei,* and *L. rhamnosus*), while it had no effect on survival post MI, was associated with improved ejection fraction in antibiotic treated animals versus controls. Probiotic treatment was also associated with both increased levels of myeloid cells in the hearts of antibiotic treated mice and enhanced propionate levels, and some of these effects were recapitulated with propionate supplementation alone. This work expands upon our understanding of the links between gut microbiota, the immune system and myocardial repair after injury.

Clinical intervention trials targeting microbiota for the treatment of CVD have mainly involved antibiotics for *Chlamydia pneumoniae*, driven by epidemiological and mechanistic links between this organism and CVD. Results from these studies have been disappointing, with chronic antimicrobials proving to be ineffective in preventing secondary CVD events[1]. Few studies have assessed the impact of antibiotics on ventricular remodelling in the immediate post MI setting. One potential exception to this was the ‘PROVE IT-TIMI22 trial’, in which long-term treatment with gatifloxasin vs placebo was evaluated for the prevention of major adverse cardiovascular events in subjects with recent acute coronary syndrome[8]. No effects on either cardiovascular events or mortality were observed with antibiotics. An alternative study, the ‘TIPTOP trial’, was a single center open-label,

randomized intervention trial in which patients with ST-segment elevation MI and left ventricular dysfunction were randomized to doxycycline for 7d in addition to standard therapy versus standard care. Significant improvements in left ventricular end diastolic volume index, infarct size, and severity at 6 months post intervention were noted amongst the doxycycline recipients[9]. The mechanistic rationale attributed to the beneficial effects was that matrix metalloproteinase-inhibiting properties of doxycycline may have attenuated adverse ventricular remodeling[9]. In contrast, the studies by Hsieh and colleagues used a cocktail of poorly absorbed broad-spectrum antibiotics to suppress gut microbiota[7]. This may in part account for the seemingly divergent observed effects of the antibiotic cocktail on heart function compared to results of the TIPTOP trial. In addition, the timing of antibiotic treatment in relation to MI induction may also be of importance. In this regard, little is known concerning the impact of antibiotic use prior to MI on ventricular remodelling in subjects. The animal model studies by Hsieh and colleagues suggest an intact gut microbial community is required around the time of injury for proper myocardial repair.

As noted above, antibiotics can have effects on the host beyond their anti-microbial properties. It therefore is possible that some of the adverse effects of antibiotics pre-treatment reported by Hsieh and colleagues may be independent of gut microbiota. However, the ability of fecal microbial transplantation, probiotics, or a microbiota down-stream end-product (propionate) to mitigate some of the adverse effects of antibiotics all point toward involvement of gut microbiota in myocardial repair[7]. Antibiotics in the absence of MI significantly increased systemic TNFα in their model[7], which in other studies has been associated with cardiac hypertrophy, ventricular dilatation and fibrosis. In was also of interest that the beneficial effects of SCFAs on reversing antibiotics-induced reduction in survival were incomplete (only ~50%). Hence, assuming the observed effects of antibiotics result from gut microbiota suppression, other microbial metabolites may impact cardiac repair. In fact, use of broad spectrum antibiotics to globally suppress gut microbiota theoretically would impact both potentially helpful (e.g. propionate) and harmful (e.g. TMAO) gut microbial pathways[2,3]. In addition to the strong association between TMAO and major adverse cardiac events[1–3], this metabolite has recently been implicated in HF through both human and animal model investigations[10,11]. Plasma TMAO is both increased in HF patients and associated with poorer long-term survival[10]. Animal studies have further demonstrated that targeting of the TMAO pathway through either diet or microbial enzyme inhibitors impacts ventricular remodelling in mice[11]. The adverse phenotype reported by Hsieh and colleagues argues for suppression of a beneficial effect of gut microbiota, not suppression of an adverse microbiota-dependent pathway. While not examined in their studies, secondary bile acids are yet another class of microbiota-derived metabolites with evidence for a potential role in HF. Both the composition and size of the bile acid pool are altered in HF patients[12], and in a small (n=17) prospective, double-blind, randomized, placebo-controlled crossover study, clinically stable patients with HF were reported to have modest improvements in blood flow with administration of the secondary bile acid ursodeoxycholic acid[13]. Finally, bacterial products of aromatic amino acid metabolism have been linked to the severity of MI in rats, suggesting numerous additional gut microbiota-derived metabolites may also play a role in cardiac repair[14].

In summary, the work by Hsieh and colleagues contributes to a growing body of evidence implicating gut microbiota in cardiac repair processes. These findings open the door for new treatment strategies for MI and HF, which might be anywhere along the diet->gut microbiota->host receptor/effector pathways involved.[1] The current study suggests specific probiotics, SCFAs, or other microbiota-targeted/driven interventions, warrant further investigation in human clinical intervention studies. Much work remains to prove the benefits of any of these or alternative approaches, like non-lethal small molecule inhibitors of specific microbial enzymes,[15] for the treatment of CVD and metabolic disorders. Finally, this research exposes impaired cardiac repair as yet another potential side effect of antibiotics use. Whether these findings replicate in humans is of considerable clinical interest.

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