Gut Microbiota and Atrial Fibrillation

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Atrial fibrillation (AF), despite medical and ablative therapies, remains one of the most prevalent and widespread arrhythmias affecting the quality of human life globally [1]. The heterogeneity of the underlying atrial substrate, extent of atrial fibrosis and the discrepancies among inter-individual electrophysiological characteristics contribute to unpredictable responses to drug or ablation therapy [2]. With the establishment of the heart-gut axis concept, accumulating studies suggest that the gut microbiome plays an important role in the pathogenesis of cardiovascular diseases including initiation and progression of AF. Emerging evidence suggests that through immune system and metabolic alterations, gut microbiota disequilibrium could induce obesity, HTN and T2DM, traditional cardiac risk factors that play an essential role during atrial remodeling in the development of AF [3]. Gut microbiota and its products have also been shown to have an important prognostic value in AF patients [4]. Targeted modification of gut microbiota may be a novel adjunct treatment strategy for AF and its concomitant risk factors in near future.

Numerous studies have been done to establish the possible role of gut microbiota and their metabolites in the pathophysiology of initiation and progression of AF. Studies have found that there is serious dysbiosis of the gut bacteria in patients with AF, which may play a crucial role in the pathology of atrial remodeling and the formation of an arrhythmogenic substrate [5]. Based on the significant correlation between the distinguishing metabolic features in AF and the disordered gut flora, it is possible that the gut microbiota dysbiosis induced disordered microbial functions, causing the deficiency of multiple cardiovascular-protective metabolites and thus increased susceptibility to AF. In patients with AF, selective abundance of few species of gut bacteria (*Ruminococcus, Streptococcus*, and *Enterococcus* etc.) and selective decrease of few species (*Faecalibacterium*, *Alistipes, Oscillibacter, Bilophila, Flavonifractor* etc.) have been reported in these studies [5].

Metabolites derived by the gut microbes, including trimethylamine N-oxide (TMAO) and lipopolysaccharides (LPS), have been shown to act on downstream cellular targets to prevent or contribute to the pathogenesis of structural, metabolic and functional cardiovascular remodeling [6]. TMAO facilitates the progression of AF by activating the cardiac autonomic nervous system (CANS) and pro-inflammatory pathways. In addition, the gut microbes associated with the production of TMAO are also associated with various risk factors for AF: such as metabolic syndrome and cardiovascular disease [7]. Gut-derived lipopolysaccharide (LPS) has been found to be a predictor of major adverse cardiovascular events (MACE) in patients with AF [4]. Circulating levels of LPS were higher in patients with AF compared with those with sinus rhythm and in those AF patients who experienced MACE as compared to patients without any MACE on follow-up [4]. Other metabolites like palmitic acid, niacin, choline, 3-indoleacetic acid, L-tryptophan and pyroglutamic acid etc. also have been linked with AF pathogenesis [8]. Some studies have found that metabolites like α-linolenic acid and linoleic acid exerted protective effects through inhibition of pathways which played a regulatory role in atrial fibrosis and contributed to the progression of AF [9].

Studies have also shown that in patients with AF gut microbial dysbiosis develops at an early stage in AF patients and is maintained beyond a year, indicating the possible overgrowth of a variety of harmful microbes leading to metabolic variations that might be implicated

in the arrhythmogenic substrate aggravation in the left atrium during the pathological progression of AF [8]. Stearamide, a metabolite produced microbes enriched in AF patients, was positively linked with CHA2DS2-VASc score which represents the severity of atrial remodeling in AF patients [8]. Similarly, Choline, a metabolite decreased in AF patients, was negatively linked to CHA2DS2-VASc score [8].

Future studies are needed to better understand the complex changes in the composition of the microbiota under different pathophysiological conditions and the effects of the derived metabolites on the progression of AF to identify new therapeutic and diagnostic options for the management of AF patients. Continuous feces sample collection from the patient cohort during a follow-up period, a dynamic observation of the dysbiotic gut microbial pattern might provide stronger evidence. Pre-clinical and clinical intervention studies are warranted to establish the efficacy of these interventions in humans and to check whether characterization of the gut microbiota and its derived metabolites could be used as prognostic biomarkers in AF patients. More importantly, a discriminant model based on bacterial signature profiles needs to be established with the potential to be used as biomarkers for AF in the future.

Bibliography

1. Chugh SS., *et al*. "Worldwide epidemiology of atrial fibrillation: A Global Burden of Disease 2010 Study". *Circulation* 129 (2014): 837-847.

2. Marrouche NF., *et al*. "Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study". *The Journal of the American Medical Association* 311.5 (2014): 498-506.

3. Du X., *et al*. "Is atrial fibrillation a preventable disease?" *Journal of the American College of Cardiology* 69.15 (2017): 1968-1982.

4. Pastori D., *et al*. "Gut-Derived Serum Lipopolysaccharide is Associated With Enhanced Risk of Major Adverse Cardiovascular Events in Atrial Fibrillation: Effect of Adherence to Mediterranean Diet". *Journal of the American Heart Association* 6.6 (2017): e005784.

5. Zuo K., *et al*. "Disordered gut microbiota and alterations in metabolic patterns are associated with atrial fibrillation". *Gigascience* 8.6 (2019): giz058.

6. Brown JM and Hazen SL. "Microbial modulation of cardiovascular disease". *Nature Reviews Microbiology* 16.3 (2018): 171-181.

7. WH Tang and SL Hazen. "The gut microbiome and its role in cardiovascular diseases". *Circulation* 135 (2017): 1008-1010.

8. Zuo Kun., *et al*. "Duration of Persistent Atrial Fibrillation Is Associated with Alterations in Human Gut Microbiota and Metabolic Phenotypes". *M Systems* (2019): 4.

9. Jiang M., *et al*. "ALA/LA ameliorates glucose toxicity on HK-2 cells by attenuating oxidative stress and apoptosis through the ROS/p38/TGF-beta1 pathway". *Lipids in Health and Disease* 16.1 (2017): 216.