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Editorial

Gut-microbiota derived TMAO: A risk factor, a mediator or a bystander in the pathogenesis of atrial fibrillation?

Atrial fibrillation (AF) is the most common arrhythmia and is associated with substantial morbidity and mortality [1]. AF is increasingly considered the consequence of a complex atrial cardiomyopathy due to the combined effects of genetics, risk factors and comorbidities [2]. Current pharmacological and catheter based anti-arrhythmic interventions have limited efficacy and AF-promoting atrial cardiomyopathy is often progressing despite temporally effective rhythm control. The development and the progression of atrial cardiomyopathy can be partially prevented by the treatment of concomitant conditions and management of risk factors by changes in lifestyle. Physical activity, changes in diet and weight loss have been shown to control sinus rhythm and current AF guidelines [3] now recommend risk factor modification as an important component of rhythm control strategies in AF patients.

Changes in lifestyle and diet have been related to alterations in gut microbiota [4]. The gut microbiota is a dynamic ecosystem of commensal, symbiotic and pathogenic microorganisms that influence host health by producing bioactive metabolites. The human body consists of about 100 trillion microbial cells [bacteria, viruses, archaea and eukaryotes] and 20 million microbial genes that outnumber by about 10–1000 times the number of human cells and genes, respectively [5]. In recent years, growing evidence has demonstrated that interventions directed at gut microbiota may play a critical role in many cardiovascular diseases including heart failure, hypertension, and coronary artery disease [6]. Therefore, therapeutic targeting of gut microbiota may contribute to a better AF control by affecting multiple risk factors of AF. One key product of gut microbiota is trimethylamine [TMA] which is produced from dietary choline and carnitine [from meat and dairy products]. TMA *N*-oxide [TMAO] is a product of TMA oxidization by liver flavin-containing monooxygenase enzyme and the most extensively studied microbial metabolite involved in AF pathogenesis [7–10].

In this issue of the journal Nguyen et al. [11] assessed the levels of TMAO in 56 patients with paroxysmal AF in comparison to 22 patients with persistent [<1 year] AF in whom a rhythm control strategy was preferred. The authors detected a significant correlation between the levels of TMAO and AF progression phenotypes without difference in precursor levels [betaine, choline and L-carnitine]. These findings confirm the previously reported positive correlations between TMAO and AF [7–10] and add additional information about the association between TMAO levels and AF progression.

The study has some limitations that need consideration when interpreting the results. The authors did not include a control group in sinus rhythm. Therefore, the role of increased TMAO levels in AF patients remain unclear and requires further investigation. Also, the study population is very small, which raises serious concerns about the putative predictive value of TMAO for AF. In addition, given the higher comorbidity burden in persistent compared to paroxysmal AF patients and the multiple lines of evidence that TMAO is associated with increased risk of pre-clinical and clinical coronary artery disease [12], hypertension [13] and heart failure [14], the difference in TMAO level could be a result from the concomitant comorbidities rather than from AF itself. Clearly, randomized clinical trials or larger observational studies with propensity score matching are required to demonstrate and validate the putative effect of TMAO on AF type and AF progression. Overall, despite the many evidence, it is still unclear whether TMAO is a risk factor, a mediator or a bystander in the disease process.

The putative mechanisms of TMAO action potentially promoting AF are incompletely understood. In a canine model local injection of TMAO into four major anterior right ganglionated plexi enhances neural activity via activation of p65 nuclear factor kappa-light-chain-enhancer of activated B cells pathway and increases the expression of c-fos and nerve growth factor. TMAO also prevents the rapid atrial pacing-induced shortening of the atrial effective refractory period, thereby reducing the likelihood of reentry and the vulnerability to AF [15]. Neonatal rat cardiomyocytes exposed to TMAO show increased mRNA and protein levels of hypertrophy markers such as atrial natriuretic peptide, beta-myosin heavy chain along with more fibrosis via unregulated transforming growth factor β1/Smad3 signaling pathways. Rats treated with intraperitoneal TMAO injection for 1–2 weeks reveal increases in left ventricular wall dimensions along with an enhanced expression of hypertrophy markers, increased cardiomyocyte size and interstitial fibrosis [16]. Finally, neonatal cardiac fibroblasts exposed to increasing concentrations of TMAO for 24 h show oxidative stress and increases of NOD-, LRR- and pyrin domain-containing protein 3 [NLRP3] inflammasome activity, a caspase-1 platform responsible for the maturation of interleukins-1β [IL-1β] and IL-18 [17], which has been casually associated with the development and progression of AF [18,19]. Thus, TMAO could be an upstream activator of the NLRP3 system, a hypothesis that requires direct verification.

In conclusion, recent research has provided important information on risk factors and the mechanisms contributing to AF, but

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many unresolved issues and translational challenges remain [20,21]. Although there is some preclinical and clinical evidence for a potential role of TMAO in AF pathophysiology, further experimental and clinical work is needed to validate the causal relationship between gut microbiota and its metabolites and AF and to delineate the underlying mechanisms of interaction.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Monika Gawałko [a,b,c]
Dominik Linz [c,d,e,f]
Dobromir Dobrev [a,g,h,*]

[a] *Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Germany*

[b] *1st Department of Cardiology, Medical University of Warsaw, Warsaw, Poland*

[c] *Department of Cardiology, Maastricht University Medical Centre and Cardiovascular Research Institute Maastricht, Maastricht, The Netherlands*

[d] *Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

[e] *Centre for Heart Rhythm Disorders, Royal Adelaide Hospital, University of Adelaide, Adelaide, Australia*

[f] *Department of Cardiology, Radboud University Medical Centre, Nijmegen, The Netherlands*

[g] *Montréal Heart Institute and University de Montréal, Medicine and Research Center, Montréal, QC, Canada*

[h] *Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, USA*

* Corresponding author at: Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Hufeland-strasse 55, 45122 Essen, Germany.
E-mail address: dobromir.dobrev@uk-essen.de (D. Dobrev)