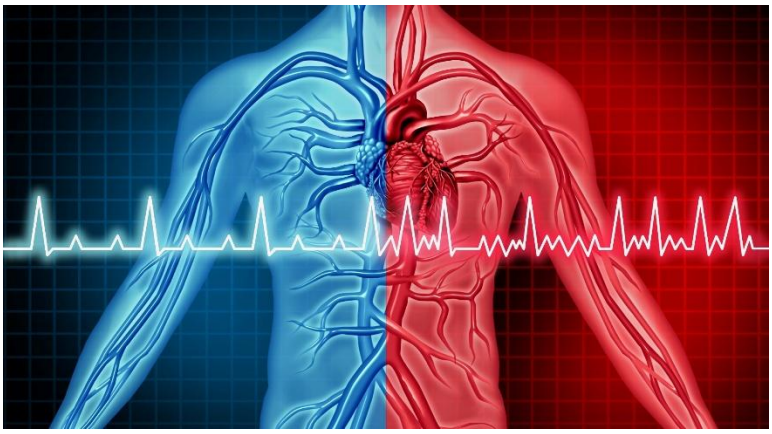
Atrial Fibrillation Linked to a Common Dietary Nutrient Feeds a Gut Pathway

A recent study published suggests that trimethylamine N-oxide (TMAO), produced when gut microbes convert nutrients such as choline into trimethylamine (TMA), which is then oxidized in the liver, is independently associated with prevalent atrial fibrillation (AF) in humans and may promote AF susceptibility, onset, and progression in mice. By inhibiting muscarinic receptor 2 signaling, TMAO may disrupt autonomic regulation, with increased sympathetic tone proposed as one mechanism contributing to AF. These findings suggest that diet, through its effects on the gut microbiome and TMAO production, may influence AF susceptibility, although dietary effects were tested only in mice, and the human findings came from a cardiovascular referral cohort.

AF remains a major contributor to cardiovascular disease (CVD)-related illness and death worldwide. Elevated TMAO levels have been associated with CVD-related changes, including cardiac fibrosis and inflammation. However, the biological mechanisms through which TMAO may promote AF remain unclear. An improved understanding of the gut microbiome-related changes that influence AF development could help researchers develop more targeted treatments to reduce the global burden of AF and CVD. Future studies will need to determine whether therapeutic strategies targeting TMAO can safely reduce AF and how differences in gut microbiome composition, liver metabolism, and kidney filtration affect circulating TMAO levels.



Study

In the present study, researchers investigated whether TMAO generated through the gut microbiome could promote AF development. To do so, they quantified TMAO, choline, and betaine levels in plasma samples obtained from 5,090 individuals from the Cleveland Clinic GeneBank who were undergoing elective cardiac catheterization, using liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS). Individuals with a myocardial infarction during the preceding four weeks or elevated troponin I at enrollment were excluded.

The team also used genetically engineered mice expressing the CREM-IbΔC-X variant of the human cyclic adenosine monophosphate (cAMP) response element modulator gene to investigate AF development. These animals received TMAO- or choline-supplemented diets in separate experiments. The researchers conducted transesophageal electrical pacing studies to determine AF inducibility among wild-type C57BL/6J mice fed TMAO-supplemented or standard diets. They placed electrodes in the esophagus of the animals to deliver electrical impulses and promote arrhythmias in the heart. They separately used serial needle-electrode

electrocardiograms (ECGs) to monitor the first onset of paroxysmal AF and progression to persistent AF, defined as AF detected across 10 consecutive ECG recordings, in CREM-IbΔC-X mice receiving different diets, with wild-type mice included in separate control experiments.

The team also explored the effects of iodomethylcholine (IMC), a selective inhibitor of choline trimethylamine-lyase (CutC/D), on TMAO levels. They analyzed microbial DNA from cecal samples, used echocardiography to assess the effects of choline and IMC on cardiac structure, and performed cardiac electrical mapping to examine the electrophysiological effects of choline supplementation. They exposed human and murine cardiac cells, including fibroblasts and cardiomyocytes, to physiologically relevant TMAO levels and examined interleukin-1β (IL-1β) and NLRP3 expression. They also performed murine ECG experiments using MCC950, a chemical compound that inhibits the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome.

The researchers used logistic regression to estimate odds ratios (ORs) for prevalent AF. The models accounted for variables such as age, sex, smoking habits, comorbidities, and laboratory findings, including high-sensitivity C-reactive protein (hs-CRP) and estimated glomerular filtration rate (eGFR).

Findings

The team found that plasma TMAO, betaine, and choline levels were independently and significantly associated with AF prevalence. For TMAO, the adjusted odds ratio comparing the highest with the lowest concentration tertile was 1.7 (95% confidence interval, 1.3-2.1). The TMAO- or choline-supplemented CREM-IbΔC-X mice developed AF earlier than chow-fed controls, without significant differences in body mass or appreciable liver-related pathologies.

The genetically modified animals also showed higher plasma TMAO levels after choline supplementation. These findings suggest that TMAO may contribute to AF onset and progression in mice, and that reducing gut microbial production of TMAO may help lower AF susceptibility in this model. Mice fed TMAO diets showed an increased likelihood of developing AF in the transesophageal pacing study. In fact, mice receiving TMAO supplementation showed an 11-fold increase in AF inducibility in both sexes compared with controls.

Choline supplementation altered the structure and function of the heart. Left atrial size was significantly increased at five and eight weeks, while IMC treatment attenuated the enlargement at eight weeks. In choline-supplemented mice, optical mapping revealed a nonsignificant reduction in conduction velocity but significantly shortened action-potential duration at 80% repolarization and reduced cardiac wavelength. In HEK293 cells engineered to express muscarinic receptor 2 (M2R), TMAO inhibited receptor signaling in the presence of the M2R agonist carbachol. Together with higher heart rates in choline-fed mice, this finding supported a possible role for autonomic dysfunction in promoting AF, although sympathetic activity was not directly measured.

While choline accelerated AF onset, IMC treatment delayed the onset of paroxysmal and persistent AF and reduced TMAO levels by suppressing the microbial conversion of choline to TMA under both aerobic and anaerobic conditions, thereby reducing subsequent TMAO formation in the liver. Choline altered gut microbial communities in association with AF. IMC, on the other hand, attenuated these changes by reversing the loss of gut microbiome diversity and reducing the choline-associated increase in overall Firmicutes abundance, although individual

species showed differing patterns. An exploratory analysis also linked Parvibacter caecicola to the timing of paroxysmal AF onset in mice, although the authors noted that this association requires further investigation. TMAO also did not increase NLRP3 or IL-1β expression at physiologically relevant concentrations, and MCC950 did not delay AF development, suggesting that NLRP3 inflammasome activation was not a major mechanism in this mouse model.

Conclusion

The findings demonstrate that higher plasma TMAO levels were independently associated with prevalent AF in humans, whereas direct TMAO exposure or gut microbial production of TMA from dietary choline promoted AF onset and progression in mouse models. However, the human analysis was observational and assessed existing rather than incident AF, while the mechanistic and therapeutic findings came from mice and cell experiments. No human dietary or IMC intervention was tested, and AF recurrence following IMC withdrawal was not examined.

Together, the preclinical findings support clinical investigation of TMAO-lowering approaches as potential strategies for AF prevention. In future studies, researchers should explore different molecules that can reduce TMAO levels and determine how gut microbiome composition, hepatic FMO3 activity, and renal clearance influence circulating TMAO levels and treatment responses in humans.

Source:

https://www.news-medical.net/news/20260727/A-common-dietary-nutrient-feeds-a-gut-pathway-linked-to-atrial-fibrillation.aspx