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Conference Abstract

YI 1.4 Increases in Circulating Trimethylamine-*N*-Oxide Contribute to the Development of Age-Related Aortic Stiffness in Humans and Mice

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ABSTRACT

Age-related increases in aortic stiffness, assessed by pulse wave velocity (PWV), predict cardiovascular (CV)-related mortality, but the upstream drivers are incompletely understood.

Purpose: To determine if higher circulating levels of the gut microbiome-derived metabolite trimethylamine-*N*-oxide (TMAO) contribute to age-related aortic stiffening.

Methods and Results: Plasma TMAO concentrations were higher in healthy middle-aged-to-older (45–79 y; $N = 83$) vs. young (18–27 y; $N = 14$) humans (6.3 ± 0.6 vs. 1.8 ± 0.3 μM; $p < 0.01$) and positively related to carotid-femoral (c-f) PWV ($r^2 = 0.15$, $p < 0.0001$). To determine the role of TMAO in established age-related aortic stiffness, we supplemented old mice (27 mo; $N =$ 12–16/group) with 1% 3,3-dimethyl-1-butanol (DMB; suppresses microbiota-dependent TMAO production) in drinking water for 8–10 weeks vs. normal drinking water (control). Relative to young mice (3 mo; $N = 23$), old mice had higher aortic (a) PWV (412 ± 17 vs. 349 ± 11 cm/s; $p < 0.01$), but DMB had no effect on aPWV ($p = 0.58$ vs. control) despite suppressing plasma TMAO (control: 8.7 ± 6.3 vs. DMB: 4.3 ± 1.2 μM, $p = 0.07$) to young levels (3.8 ± 2.6 μM). Next, to determine if TMAO contributes to the development of aortic stiffening, we initiated DMB at mid-life (18 mo; i.e., before the onset of stiffening; $N =$ 8–21/age/treatment). aPWV was similar between young and 18 month-old mice (363 ± 5 cm/s; $p = 0.58$), but increased progressively with age in control mice (24 mo: 401 ± 13 cm/s, $p = 0.03$ vs. young; 27 mo: 442 ± 10 cm/s, $p < 0.001$ vs. young), whereas age-related increases in PWV were considerably attenuated by DMB (24 mo: 359 ± 9 cm/s; 27 mo: 388 ± 10 cm/s, both $p < 0.01$ vs. control).

Conclusions: Age-related increases in TMAO contribute to the development of aortic stiffness. TMAO-targeted interventions initiated in mid-life may prevent/delay age-related aortic stiffening and reduce CV risk.

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