



## 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 ( $6.3 \pm 0.6$  vs.  $1.8 \pm 0.3$   $\mu\text{M}$ ;  $p < 0.01$ ) 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 ( $412 \pm 17$  vs.  $349 \pm 11$  cm/s;  $p < 0.01$ ), but DMB had no effect on aPWV ( $p = 0.58$  vs. control) despite suppressing plasma TMAO (control:  $8.7 \pm 6.3$  vs. DMB:  $4.3 \pm 1.2$   $\mu\text{M}$ ,  $p = 0.07$ ) to young levels ( $3.8 \pm 2.6$   $\mu\text{M}$ ). 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 ( $363 \pm 5$  cm/s;  $p = 0.58$ ), but increased progressively with age in control mice (24 mo:  $401 \pm 13$  cm/s,  $p = 0.03$  vs. young; 27 mo:  $442 \pm 10$  cm/s,  $p < 0.001$  vs. young), whereas age-related increases in PWV were considerably attenuated by DMB (24 mo:  $359 \pm 9$  cm/s; 27 mo:  $388 \pm 10$  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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