

Lifelong dietary omega-3 fatty acid reverses cardiac and vascular dysfunction via MMP-2 modulation in aged mice

S.S. Saeedi Saravi, N.R. Bonetti, A. Vukolic, L. Liberale, D. Vdovenko, T.F. Luscher, G.G. Camici, J.H. Beer

University of Zurich, Schlieren, Switzerland

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Background: Aging has a remarkable effect on the cardiovascular system, and negatively causes structural and functional changes in the heart including diastolic/systolic dysfunction and left ventricular (LV) dyssynchrony, as well as, arterial stiffness which may develop to heart failure with preserved ejection fraction (HFpEF) in aged adults. We recently showed that the plant-derived omega-3-fatty-acid α -linolenic-acid (ALA) has emerged to confer potential protective effects against cardiovascular disease. Since cardiovascular aging is a chronic process, we hypothesized that a lifelong effective dietary supplementation with ALA will reverse or prevent age-related diastolic and arterial dysfunction during aging.

Purpose: Here, we test the hypotheses that (1) lifelong dietary ALA will prevent LV diastolic and arterial dysfunction in aged mice and that (2) lifelong dietary ALA will prevent the age-related cardiovascular dysfunction through modulation of matrix-metalloproteinase-2 (MMP-2) in the heart and arteries.

Methods and results: 6-month-old (young) wild-type C57BL/6J mice were fed a low (0.03%), as control, or high ALA (7.3%) diet for more than 12

months. Our results show that aged (>18 months) mice on low ALA diet recapitulate major hallmarks of HFpEF, including diastolic dysfunction with preserved left ventricular ejection fraction, cardiac interstitial fibrosis, impaired acetylcholine-induced relaxation of aortic segments, and arterial stiffness. Intriguingly, we revealed that lifelong ALA-rich diet prevents diastolic dysfunction, vascular relaxation capacity, reduced pulse wave velocity, interstitial fibrosis, and coincident hemodynamic abnormalities in aged mice. Lifelong dietary ALA-in the prevention strategy-was associated with remarkably reduced cardiac and aortic MMP-2 and COX-2 expression, lower levels of pro-inflammatory cytokine TNF- α , and increased isocitrate dehydrogenase 2 (I α h2) expression, decreased function of which has previously been associated with cardiac dysfunction.

Conclusions: Our data support that lifelong ALA-rich diet restores normal cardiac and vascular function in aged mice with LV diastolic and arterial dysfunction and prevents development of age-related cardiovascular dysfunction through the modulation of MMP-2 signaling.