Comparative cardiovascular and respiratory physiology

The bottlenose dolphin (*Tursiops truncatus*): A novel model for studying healthy vascular aging

Yara Bernaldo De Quiros Miranda, Sophia Mahoney, Nicholas VanDongen, ... See all authors

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Abstract

Aging is the primary non-modifiable risk factor for the development of cardiovascular diseases (CVD). CVD are often preceded by arterial dysfunction, including endothelial dysfunction and aortic stiffening. Our preliminary results suggest that the circulating milieu is

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associated with differences in arterial function in young and mid-life/older (ML/O) adults. Moreover, incubation of mouse arteries with serum from young and ML/O adult humans can directly transfer arterial aging phenotypes for endothelial function and aortic stiffness. These results suggest that age-related changes in the circulating milieu are an underlying mechanism of age-related arterial dysfunction. Dolphins are mammals that have evolutionary adapted to diving, with constant cycles of tissue hypoxia/reoxygenation and disturbed shear stress -- exposures which cause arterial dysfunction in humans. Dolphins also have long lifespans and are relatively free of CVD. Taken together, dolphins may be a unique model of healthy vascular aging, with possible applications to clinical medicine. PURPOSE: To determine if the serum of bottlenose dolphins (*Tursiops truncatus*) induces the same arterial aging phenotypes as the serum of age-equivalent humans. Methods: Common carotid arteries and aorta rings from young (Y; 5 mo) and old (O; 25 mo) wildtype female (F) and male (M) C57BL/6N mice were exposed *ex vivo* for 24 and 48h, respectively, to 5% sex-matched adult dolphin serum. Dolphin serum of Y (17 ± 4 years; n = 16: 5F / 11 M) and ML/O (29 ± 2 years; n = 4: 1F/3M) adults was obtained from the National Marine Mammal Tissue Bank. Endothelial function was assessed as carotid artery endothelium-dependent dilation (EDD) in response to increasing doses of acetylcholine. Aortic stiffness was measured as elastic modulus, a measure of intrinsic mechanical wall stiffness. Dolphin serum-mediated responses in mouse arteries were compared with that of adult human serum data (Y, 24 ± 1 years, n=10: 5F/5M; ML/O, 67 ± 3 years, n=10: 5F/5M). Differences were assessed via 2-way ANOVAs; within

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species post hoc analyses conducted between age groups. Results: Endothelial Function. Peak EDD in Y mouse carotid arteries was lower following exposure to serum from ML/O adult humans (ML/O, 78 ± 2 v. Y, 92 ± 2%; P < 0.001) and higher in O mouse carotid arteries after exposure to Y adult serum (92 ± 2 vs. 73 ± 5%, P = 0.001). In contrast, EDD was similarly high across all groups following dolphin serum exposure (³ 93% peak EDD), independent of the age of the serum donor or the mouse arteries (Y v. ML/O serum donor in Y arteries, P = 0.773; in O mouse arteries, P = 0.942). Aortic Stiffness. Stiffness in Y aortic rings was ~60% higher following exposure to ML/O adult human serum (P = 0.001 v. Y adult serum). In O mouse aortic rings, stiffness was 25% lower after exposure to Y adult serum (P = 0.044 v. ML/O adult serum). In contrast, stiffness was similar across all groups following dolphin serum exposure, independent of age of the serum donor or the arteries (Y v. ML/O serum donor in Y aortic rings, P = 0.974; in O aortic rings P = 0.157). CONCLUSIONS: The circulating milieu of bottlenose dolphins may be geroprotective, which could serve as a model to investigate mechanisms and potential therapies for preventing adverse vascular aging and promoting CV health and longevity in humans.

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