SOD2 DEFICIENCY-MEDIATED OXIDATIVE STRESS INCREASES ARTERIAL STIFFNESS IN AGED MICE

ACC Poster Contributions
Ernest N. Morial Convention Center, Hall F
Monday, April 04, 2011, 3:30 p.m.-4:45 p.m.

Session Title: Progenitor Cells, Endothelial Cells and Vascular Disease
Abstract Category: 8. Vascular Biology/Atherosclerosis/Thrombosis/Endothelium
Session-Poster Board Number: 1108-119

Authors: Ruihai Zhou, Aleksandr E. Vendrov, Igor Tchivilev, Xi-Lin Niu, Kimberly C. Molnar, Nageswara R. Madamanchi, Marschall S. Runge, McAllister Heart Institute and Division of Cardiology, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Increased arterial stiffness, common with aging, is associated with higher risk of cardiovascular disease mortality and morbidity. While the precise signals are yet to be elucidated, increased oxidative stress is postulated to cause age-related vessel wall alterations. To test this postulate, we quantified arterial stiffness by measuring aortic pulse wave velocity (PWV) and examined oxidative stress-regulated cell signaling in aortic VSMC of young (4 mon) and aged (16 mon) C57BL/6 mice with normal (WT) or reduced expression (SOD2+/-) of SOD2, a critical antioxidant enzyme.

Methods: Aortic PWV was measured by Doppler. Gene expression in arterial wall cells and VSMC was measured by immunohistochemical and Western blot analyses and quantitative real-time PCR. Matrix metalloproteinases-2 (MMP-2) activity was analyzed by zymography.

Results: Aortic PWV, similar in WT and SOD2+/- mice at 4 mon, was increased significantly in 16 mon SOD2+/- mice (P<0.05). Aortic collagen expression was increased and elastic lamellae integrity was decreased in 16 mon old SOD2+/- mice. Protein and mRNA expression of type I collagen increased significantly whereas that of elastin decreased significantly in SOD2+/- VSMC (both 4 and 16 mon) versus WT VSMC. Elastolytic MMP-2 activity was also increased in 4 and 16 mon old SOD2+/- VSMC. SOD2+/- VSMC were prone to apoptosis as indicated by increased caspase-3 activities. SOD2+/- VSMC had increased α-actin and α-tubulin expression versus WT VSMC indicating intrinsic changes in VSMC. Insulin-like growth factor 1 induced phosphorylation of Akt and its downstream transcription factor, FoxO3a, were attenuated in SOD2+/- versus WT VSMC. Adenoviral overexpression of dominant-negative FoxO3a reversed the changes in collagen and elastin expression in SOD2+/- VSMC.

Conclusions: SOD2 deficiency dysregulated arterial wall extracellular matrix homeostasis and increased arterial stiffness, but only in aged mice. Our results suggest that impaired arterial compliance, in part, results from SOD2 deficiency in VSMC and its interaction with aging and approaches to increase SOD2 expression may offer therapeutic intervention for age-related arterial stiffening.