Impact of endothelial dysfunction on hemodynamics and collagen fiber orientation during age-related vascular remodeling

Liya Du[1], Dara Azar[1], Dorsa Eliadorani[2], Tarek Shazly[1], Susan Lessner[1,3]

1. University of South Carolina, Biomedical Engineering Program, Columbia, SC 29208 USA
2. University of South Carolina, Chemical Engineering, Columbia, SC 29208, USA
3. University of South Carolina, School of Medicine, Columbia, SC 29208, USA

Introduction: Loss of endothelial-derived nitric oxide (NO) is defined as "endothelial dysfunction," a condition that precedes or accompanies several cardiovascular pathologies associated with aging. We hypothesize that decreased NO production may lead to alterations in hemodynamic parameters, induce collagen fiber reorientation, and increase collagen production, to shift load from smooth muscle cells to the extracellular matrix, leading to vascular remodeling. The aim of this project is to study the impact of NO deficiency on hemodynamic parameters and collagen fiber angle orientation during age-related vascular remodeling using a mouse model.

Methods: We used groups of endothelial NO synthase (NOS3) knockout (KO), NOS3 heterozygous (Het), and wild type (WT) B6 mice (controls) to study the time course of vascular remodeling between 6 wks to 12 mo. In-vivo hemodynamic factors including blood pressure (BP) and volumetric flow rate were tracked at each time point. Diameter and blood velocity in mouse descending thoracic aorta (DTAo) and abdominal aorta (AAo) were measured by ultrasound to obtain volumetric flow rates. Mouse BP was monitored by tail-cuff plethysmography. We used multiphoton second harmonic generation microscopy to image collagen fibers through the wall thickness of DTAo and AAo. Circumferential (0°) and axial (90°) directions were defined by the average orientation of smooth muscle cell and endothelial cell nuclei, respectively. An image-processing protocol was then developed to reconstruct collagen fibers in 3D space. Reconstructed fibers were used to obtain fiber undulation and fiber angle distribution.

Results: In preliminary results, we found that BP in NOS3 KO mice is significantly higher than in either Het or WT mice. BP significantly increases with time in NOS3 KO mice, while there are no significant differences with age in Het or WT mice. Based on ultrasound data, aortic diameter and blood flow of DTAo in KO mice are significantly lower than those of WT mice. Aortic diameter and blood flow significantly increase with time in both Het and WT mice. Additionally, preliminary quantitative analysis of adventitial collagen fiber showed that collagen fibers are less undulated in DTAo of Het mice than WT for 3mo time point (at least 10% increase in number of fibers with stretch ratio< 1.06 for Het).