

ABSTRACT  
QUANTIFYING THE IMPACT OF ALTERED HEMODYNAMICS AND  
VASCULAR BIOMECHANICS TO CHANGES IN STRUCTURE AND FUNCTION  
IN NATIVE AND CORRECTED AORTIC COARCTATION

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Coarctation of the aorta (CoA) is associated with substantial cardiovascular morbidities despite successful treatment through surgical or catheter-based intervention. Although specific mechanisms leading to these morbidities remain elusive, abnormal hemodynamics and vascular biomechanics are implicated. We used a novel animal model that facilitates quantification of CoA-induced hemodynamic and vascular biomechanics alterations and their impact on vascular structure and function, independent of genetic or confounding factors. Rabbits underwent thoracic CoA at 10 weeks of age (~9 human years) to induce a 20 mmHg blood pressure (BP) gradient using permanent or dissolvable suture thereby replicating untreated and corrected CoA. Computational fluid dynamics (CFD) was performed using subject-specific imaging and BP data at 32 weeks to quantify velocity, strain, and wall shear stress (WSS). Vascular structure and function were evaluated at proximal and distal locations by histology, immunohistochemistry, and myograph analysis.

Results revealed proximal systolic and mean BP was elevated in CoA compared to corrected and control rabbits leading to vascular remodeling, endothelial dysfunction proximally and distally, and increased stiffness and reduced active force response proximally. Corrected rabbits had reduced but significant medial thickening, endothelial dysfunction, and stiffening limited to the proximal region despite 12 weeks of alleviated systolic and mean BP (~4 human years) after the suture dissolved. Proximal arteries of CoA and corrected groups demonstrated increased non-muscle myosin expression and decreased myosin heavy chain expression, and this dedifferentiation may influence vascular remodeling and aortic stiffening. CFD analysis of untreated CoA rabbits demonstrated significantly reduced WSS proximal to CoA and markedly elevated WSS distally due to the presence of a stenotic velocity jet. Results from corrected rabbits indicate the velocity jet may have persistent effects on hemodynamics, as WSS remained significantly reduced. These hemodynamic and morphological observations are consistent with alterations in human patients.

Using these coupled imaging and experimental results, we may determine changes in structure and function specific to CoA and correction and how they are influenced by hemodynamics and vascular biomechanics. We are now poised to augment clinical treatment of CoA through several methods, including investigation of specific cellular mechanisms causing morbidity in CoA and the development of therapies to improve endothelial function and restore vascular stiffness.