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Conference Abstract

P.58 Genetic Background Dictates Aortic Fibrosis in Hypertensive Mice

Bart Spronck[1,2,*], Marcos Latorre[1], Sameet Mehta[3], Alexander W. Caulk[1], Abhay B. Ramachandra[1], Sae-Il Murtada[1], Alexia Rojas[1], Chang-Sun He[4], Bo Jiang[4], Mo Wang[4], Matthew R. Bersi[5], George Tellides[4,6], Jay D. Humphrey[1,6]

[1]*Department of Biomedical Engineering, Yale University*
[2]*Department of Biomedical Engineering, Maastricht University*
[3]*Department of Genetics, Yale School of Medicine*
[4]*Department of Surgery, Yale School of Medicine*
[5]*Department of Biomedical Engineering, Vanderbilt University*
[6]*Vascular Biology and Therapeutics Program, Yale School of Medicine*

Keywords

Stiffness
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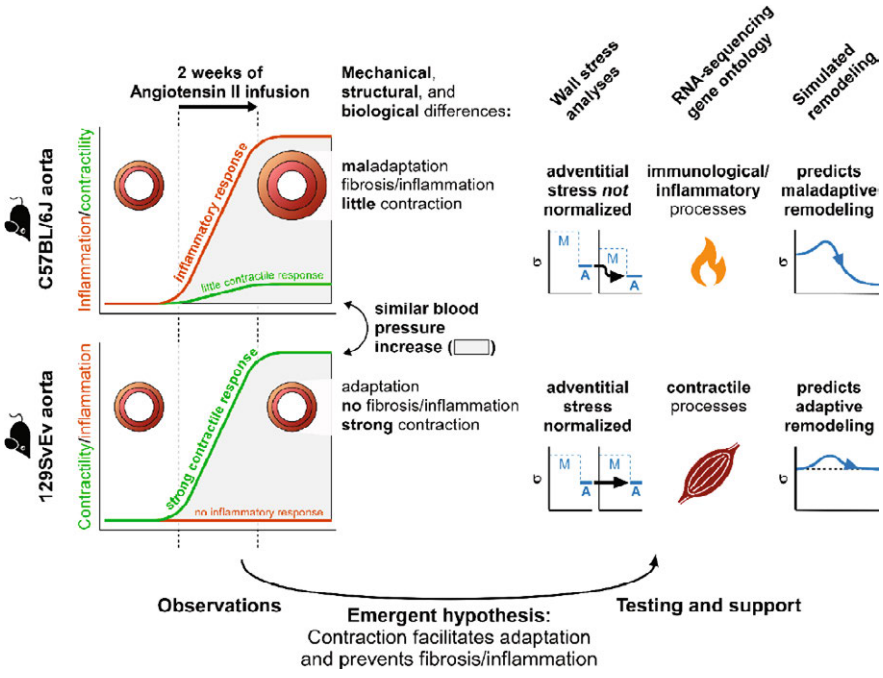
ABSTRACT

Background: Many genetic mutations affect aortic structure and function in mice, but little is known about the influence of background strain. We compared the biomechanical, structural, and gene expression responses of C57BL/6J and 129SvEv aortas to angiotensin II (AngII)-induced hypertension.

Methods: After AngII infusion (14-day, 1000 ng/kg/min) and euthanasia, excised thoracic aortas were characterized functionally using isobaric vasoactive and cyclic passive stiffness tests. Immunohistochemistry quantified medial/adventitial composition and infiltration of pan-inflammatory $CD45^+$ cells. RNA sequencing-based gene ontology, wall stress analyses, and growth and remodeling (G&R) simulations were performed to complement our mechanical findings.

Results: Baseline aortic geometry, composition, and biomechanical properties, as well as AngII-induced blood pressure increases (+34% vs. +32%, systolic), were similar across strains. Yet, AngII-induced aortic remodeling differed dramatically, with gross maladaptive, fibrotic remodeling (exuberant medial/adventitial thickening) in C57BL/6J but not in 129SvEv mice (+89% vs. +12% thickness increase, $p = 0.022$). $CD45^+$ cell density was markedly higher in hypertensive C57BL/6J than 129SvEv aortas ($p = 0.001$), while vasoconstrictive responses to AngII (causing a wall stress decrease $\Delta\sigma$) were greater in 129SvEv than C57BL/6J mice, both before ($\Delta\sigma = -8$ vs. -24%, $p = 0.023$) and after ($\Delta\sigma = -24$ vs. -46%, $p < 0.001$) hypertension. Gene expression, stress analyses, and G&R simulations reinforced the emergent hypothesis that mechanical stress-mediated immune processes promote maladaptive remodeling while smooth muscle contractile processes reduce wall stress and thereby protect against fibrosis (Figure).



*Corresponding author. Email: bart.spronck@yale.edu

Conclusions: Differentially expressed mechano-sensitive genes play key roles in the distinct hypertensive aortic remodeling in C57BL/6J and 129SvEv mice and must be considered when comparing studies in different background strains.