Circulation

FULL ACCESS | ABSTRACT

ARTERIOSCLEROSIS, THROMBOSIS, VASCULAR BIOLOGY
SESSION TITLE: VASCULAR REPROGRAMING AND REGENERATION

Abstract 13262: Improved Rabbit Model of Calcific Aortic Valve Disease Induces Severe Medial Calcification and Stenosis Equivalent to Human Disease

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Abstract

Introduction: Accurate animal models of calcific aortic valve stenosis (CAVS) are needed to get insights into the early stages. We had previously modified a rabbit model to achieve CAVS. Here, we sought to assess its ability to produce similar lesion to humans.

Methods: New Zealand rabbits were randomized to normal diet or +1% cholesterol + 3500 I.U.s/kg Vitamin D2 daily. Aortic valve area was assessed with echocardiography. At 7 weeks, blood serum and valve cusps were retrieved from sacrificed animals. Valve cusps were ex-vivo imaged with 18F-NaF microPET/CT, snap-frozen or formalin-fixed. Cusps were homogenized with an optimized protocol. Pyrophosphate (PPi) was measured in serum and cusps, metabolites analyzed with LC-MS/MS. Phosphatase activity was detected with BCIP/NBT assay. Protein content was analyzed with immunohistochemistry, quantitative ELISA and proteomics analysis (LC-MS/MS), and compared to human databases. Fixed cusps were analyzed using FT-IR and imaged with atomic force, scanning and transmission electron microscope. EDX chemical maps were obtained from the regions of interest

Results: Vitamin D and metabolites were validated in serum and tissue. Echocardiography confirmed significant valve stenosis. Sodium fluoride activity was quadrupled in experimental valves. Histology revealed severe medial calcification, positive for osteopontin, negative for TNAP, BSPII and osteocalcin. Endogenous phosphatase activity colocalized with calcification in the medium. Serum PPi levels were increased, and tissue PPi levels were decreased. Proteomics analysis revealed 96 differentially expressed proteins validating important proteins, including apolipoproteins, complement, osteonectin, matrix Gl(a), galectin-3, fetuin-A, sortiltin,

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Conclusions: The improved high-fat - vitamin D toxicity rabbit model produced severe phosphate-induced CAVS, with similar protein and ultrastructural content to human disease, related to TGF-b pathway. Further investigations are needed in the underlying molecular networks driving the lesion.

Footnotes

Author Disclosures: For author disclosure information, please visit the AHA Scientific Sessions 2021 Online Program Planner and search for the abstract title.

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