

P173. Elastin Haploinsufficiency Results In Latent Aortic Valve Disease

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OBJECTIVES: Elastin is an extracellular matrix (ECM) protein component of heart valves. Based on findings in a patient with valve disease and elastin haploinsufficiency, we hypothesized that elastin deficient mice (Eln+/-) would manifest viable heart valve disease.

METHODS: Mice were analyzed at neonatal, juvenile, adult and aged adult stages. Histochemistry, immunohistochemistry, electron microscopy, and gene expression profile analysis (Affymetrix Mouse Genome 430 2.0 Array) were performed. Aortic mechanical properties were assessed over time (TestResources). Valve structure and function was evaluated in vivo using echocardiography (Visual sonics Vevo 770).

RESULTS: Histochemical and morphometric analyses demonstrated normal valve morphology at birth, but progressive cusp thinning and elongation with proteoglycan overgrowth of the annulus. Increased valve interstitial cell (VIC) proliferation was demonstrated in neonatal Eln+/- mice and increased VIC activation was demonstrated in neonatal and juvenile Eln+/- mice. In 1mo Eln+/- mice, ultrastructure analysis demonstrated loss of ECM stratification, separated collagen bundles and increased proteoglycans; mechanical testing showed increased aortic stiffness that was incrementally increased at 4mo; and gene expression profile analysis identified specific developmental, signaling and ECM protein abnormalities in aortas and aortic valves. Eln+/- mice demonstrated normal valve function by echocardiography at 1mo, and aortic valve disease in 1/6 (17%) at 2mo and 7/10 (70%) at 16mo (predominantly aortic insufficiency); the aortic valve annulus dimension was increased and the cusps prolapsed.

CONCLUSIONS: These findings establish a role for elastin in the pathogenesis of latent aortic valve disease, and identify the Eln+/- mouse as a model of viable progressive valve disease.