Cavin-1 deficiency modifies cardiac and coronary responses to stretch and ischemia by augmenting NOS activity

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Caveolae and associated caveolin and cavin proteins may govern myocardial responses to mechanical and ischemic stress, and abnormalities in these proteins are implicated in cardiac disorders. The specific roles of cavin-1 in cardiac and coronary responses to mechanical/metabolic stress, however, are unclear. Our aim was to identify the influences of cavin-1 deficiency on myocardial and coronary responses to stretch/load and ischemia-reperfusion.

Myocardial and coronary phenotypes were characterized in hearts from cavin-$1^{-/-}$ mice. Cavin-1 deletion caused a sex-dependent fall in *in vivo* cardiac function in females (~20% lower ejection fraction). While peak contractile performance appeared comparable in *ex vivo* myocardium from cavin-$1^{-/-}$ and cavin-$1^{+/+}$ mice, diastolic stiffness (stretch-dependent diastolic force) was markedly increased and Frank-Starling behavior (stretch-dependent inotropy) moderately enhanced in hearts from cavin-$1^{-/-}$ mice. These changes in stretch-dependent function were normalized by NOS inhibition with 100 μM L-NAME (and mimicked by 100 μM nitroprusside), which exposed intrinsically depressed contractility in cavin-$1^{-/-}$ hearts. Stretch-dependent efflux of intra-cellular proteins (lactate dehydrogenase, troponin I) was exaggerated and induction of brain natriuretic peptide/c-Fos inhibited in cavin-$1^{-/-}$ *vs* cavin-$1^{+/+}$ hearts, while ERK1/2 phospho-activation was unaltered. Within the coronary vasculature, cavin-$1^{-/-}$ hearts displayed increased conductance ~70% and reactive hyperemic durations ≥3-fold in an L-NAME-sensitive manner, to exaggerated the pressure-dependence of coronary flow. Myocardial dysfunction and damage following 25 min global ischemia was also impaired in cavin-$1^{-/-}$ hearts.

Thus, Cavin-1 deletion reveals key roles in NOS-dependent and -independent control of myocardial and coronary responses to stretch or ischemia, and regulation of sarcolemmal fragility/permeability.