Collagen VI and the failing heart

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Mutation of collagen VI is linked to muscular dystrophy in humans. However, little is known about its function in the heart. We have previously demonstrated increased nanoscale deposition of collagen VI within the transverse(t)-tubules leading us to hypothesize a role in their structural remodelling. Knockout of alpha 1 chain of type VI collagen (Col6A1$^{-/-}$) in mice has conveyed substantial protection against myocardial infarction (MI) induced heart failure. To investigate the role of collagen VI in the heart we have created a novel Col6A1$^{-/-}$ rat using CRISPR/Cas9 genetic engineering. Heart failure was then induced by MI in both Col6A1$^{-/-}$ and wild type rats and compared to sham-operated rats. Echocardiography demonstrated a reduced ejection fraction in sham Col6A1-/- rats compared to wild type shams (44 ± 2 % vs 56 ± 2 %, mean ± SE respectively). Moreover, the knockout conveyed no protection against heart failure showing an ejection fraction of 34 ± 4 % after MI in Col6A1$^{-/-}$ rats compared to an ejection fraction of 44 ± 4 % in wild type rats with MI. Echocardiography also showed sham Col6A1$^{-/-}$ rats had diastolic dysfunction with an increased E/A doppler signal compared to sham wild type (2.4 ± 0.3 vs 1.5 ± 0.1 respectively). To investigate the role of Ca2+ signalling in the observed cardiovascular defects cardiac myocytes were isolated from Col6A1$^{-/-}$ and wild type rats. The cardiac myocytes were loaded with the calcium indicator Fura-2 and stimulated Ca^{2+} transient recorded. This analysis demonstrated a profound change in Ca^{2+} regulation with a large increase in peak systolic Ca^{2+} in Col6A1$^{-/-}$ myocytes compared to wild type (1.8 ± 0.2 vs 1.2 ± 0.03 340/380 ratio). Caffeine induced calcium transients revealed Col6A1$^{-/-}$ myocytes had increased sarcoplasmic reticulum Ca^{2+} store (0.8 ± 0.06 vs 0.6 ± 0.03 340/340 ratio). Our results indicate that collagen VI has a role in Ca^{2+} signalling in the cardiac myocyte that may be mediated through its presence in the t-tubules.