P21. Acute loss of SERCA2 induces both diastolic and systolic myocardial failure

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Background: Reduced activity of the sarcoplasmic reticulum Ca\(^{2+}\) ATPase (SERCA2) is believed to impair myocardial contractile function. However, myocardial function is only slightly reduced by chronic loss of SERCA2, possibly due to compensatory increase in sarcolemmal Ca\(^{2+}\) cycling. The effect of an isolated reduction in SERCA2 activity on systolic and diastolic myocardial function is not known.

Hypothesis: An isolated reduction in SERCA2 activity induces both diastolic and systolic dysfunction in SERCA2 KO mice.

Methods: Deletion of the Serca2 gene was induced in the SERCA2 conditional and cardiospecific knockout mouse by i.p. injection of tamoxifen. Cardiac function was evaluated from day 0 to day 6 with a Vivid 7 echocardiograph equipped with an i13L scan-head. Protein levels of SERCA2, Na\(^+\)/Ca\(^{2+}\) exchanger (NCX), phospholamban (PLB) and serin 16 phosphorylated PLB were quantified by Western blotting. Cardiomyocytes from SERCA2 KO and control mice were isolated and loaded with fluo-4. Calcium transients and caffeine responses were recorded.

Results: Three days after induction of gene excision, the mice had impaired in vivo diastolic and systolic function. Cardiac function decreased further until day 6. SERCA2 protein was not significantly reduced at day 3, but was reduced by 15% and 35% at day 4 and 6, respectively. The level of NCX protein increased at day 6, while PLB protein abundance was unchanged. Isolated cell function was studied.

Conclusion: Deletion of the Serca2 gene leads to systolic and diastolic dysfunction, even before we can detect any significantly reduction of SERCA2 protein levels. Compensatory changes in expression of other calcium handling proteins might compensate for the reduction in SERCA2 activity from day 6 after Serca2 gene deletion.