The effect of beta adrenergic stimulation on arrhythmogenic Ca^{2+} release in ventricular cardiomyocytes with reduced SERCA2 abundance

Stokke MK[1,2], Briston SJ[3], Louch WE[1,2], Andersson KB[1,2], Christensen G[1,2], Sejersted OM[1,2], Eisner DA[3], Trafford AW[3], Sjaastad I[1,2,4]

[1] Institute for Experimental Medical Research, Oslo University Hospital, Ullevål, Oslo, Norway
[2] Center for Heart Failure Research, University of Oslo, Oslo, Norway
[3] Unit of Cardiac Physiology, University of Manchester, Manchester, United Kingdom
[4] Department of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway

Background: Heart failure patients have an increased risk of ventricular arrhythmias. This is partly because ventricular myocytes are more prone to developing arrhythmias because of altered Ca^{2+} homeostasis. One proposed mechanism for this Ca^{2+} dependent arrythmogenicity is reduced abundance of the cardiac sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2) combined with increased adrenergic stimulation. However, the individual contributions of these factors remain to be clearified.

Methods: Whole cell voltage clamp technique combined with Ca^{2+} imaging was used to study spontaneous Ca^{2+} release in isolated ventricular cardiomyocytes from mice with inducible disruption of the *Serca2* gene (SERCA2 KO) with *Serca2*$^{flox/flox}$ mice serving as controls. *In vivo* arrhythmias were recorded with telemetric ECG surveillance after i.p. injections of isoproterenol and caffeine.

Results: Six days after induction of *Serca2* gene disruption, SERCA2 protein abundance in the left ventricles of SERCA2 KO mice was 47% compared to controls. Ventricular extrasystoles occurred with lower frequency in SERCA2 KO mice, while ventricular tachycardia and ventricular fibrillation could be elicited in both groups. Arrhythmogenic Ca^{2+} release in isolated cardiomyocytes, seen as Ca^{2+} waves, occurred less often in SERCA2 KO than control myocytes, but isoproterenol increased the propensity for waves in both groups.

Conclusions: Reduced SERCA2 protein abundance and increased beta adrenergic stimulation have opposite effects on the propensity for arrhythmogenic Ca^{2+} release in ventricular cardiomyocytes: Even though reduced SERCA2 abundance decreases the propensity for developing arrhythmias, beta adrenergic stimulation can still elicit Ca^{2+} waves and ventricular arrhythmias. Further studies are needed to determine the arrhythmogenic potential of beta adrenergic stimulation in SERCA2 KO hearts, reflecting the situation in heart failure patients.