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 arrhythmogenicity 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 clarified.

**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*\(^{\text{floxflo}}\) 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, 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.