

## The effect of beta adrenergic stimulation on arrhythmogenic Ca<sup>2+</sup> release in ventricular cardiomyocytes with reduced SERCA2 abundance

Stokke MK<sup>1,2</sup>, Briston SJ<sup>3</sup>, Louch WE<sup>1,2</sup>, Andersson KB<sup>1,2</sup>, Christensen G<sup>1,2</sup>, Sejersted OM<sup>1,2</sup>, Eisner DA<sup>3</sup>, Trafford AW<sup>3</sup>, Sjaastad I<sup>1,2,4</sup>

<sup>1</sup> Institute for Experimental Medical Research, Oslo University Hospital, Ullevål, Oslo, Norway

<sup>2</sup> Center for Heart Failure Research, University of Oslo, Oslo, Norway

<sup>3</sup> Unit of Cardiac Physiology, University of Manchester, Manchester, United Kingdom

<sup>4</sup> 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<sup>2+</sup> homeostasis. One proposed mechanism for this Ca<sup>2+</sup> dependent arrhythmogenicity is reduced abundance of the cardiac sarcoplasmic reticulum Ca<sup>2+</sup> 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<sup>2+</sup> imaging was used to study spontaneous Ca<sup>2+</sup> release in isolated ventricular cardiomyocytes from mice with inducible disruption of the *Serca2* gene (SERCA2 KO) with *Serca2<sup>lox/lox</sup>* 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<sup>2+</sup> release in isolated cardiomyocytes, seen as Ca<sup>2+</sup> 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<sup>2+</sup> release in ventricular cardiomyocytes: Even though reduced SERCA2 abundance decreases the propensity for developing arrhythmias, beta adrenergic stimulation can still elicit Ca<sup>2+</sup> 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.