Swift F1,2, Birkeland JAK1,2, Tovsrud N1,2, Enger UH1,2, Aronsen JM1,2, Sjaastad I1,2,3, Sejersted OM1,2

1 Institute for Experimental Medical Research, Ullevaal University Hospital
2 Center for Heart Failure Research, University of Oslo
3 Department of Cardiology, Ullevaal University Hospital

Recent reports suggest that the α2-isoform of the NKA plays a special role in regulation of contractility in cardiomyocytes, probably through intimate crosstalk with the Na+/Ca2+-exchanger (NCX). Downregulation of the α2-isoform in cardiomyocytes from rats with congestive heart failure (CHF) could therefore importantly contribute to altered contractility. Six weeks after ligation of the left coronary artery, CHF was confirmed by haemodynamic measures and increased lung weight. Western blots of left ventricle protein homogenates showed a 74% downregulation of the α2-isoform (CHF vs. Sham, p<0.01). In voltage clamp experiments, a low dose (0.3 µM) of ouabain specifically blocked the α2-isoform. In cardiomyocytes from Sham hearts, this low dose reduced NKA current (INKA) density by 8.3%, but gave a reduction of only 2.3% in cardiomyocytes from CHF hearts. In detubulated cardiomyocytes, the low dose of ouabain reduced the INKA by 4.0% in Sham, but there was no significant reduction in CHF, indicating that the loss of the α2-isoform occurs mainly in the t-tubules. In Sham, abrupt activation of INKA led to a decrease in NCX current (INCX), presumably due to local depletion of [Na+]i in the vicinity of NCX. This decrease was smaller when the α2-isoform was downregulated (CHF) or inhibited (ouabain in Sham), indicating that the α2-isoform is necessary to modulate local [Na+]i close to NCX. Despite the apparent low abundance of α2-isoforms, blockade by ouabain increased contractility by 31±5% in Sham, but by only 15±5% in the CHF group.

We conclude that downregulation of the α2-isoform in the t-tubules causes attenuated control of NCX activity in CHF, leading to Ca2+ mismanagement.