of Dvl-1 tended to be decreased in ICM (0.63; p < 0.005) as well Fzd-7 in ICM and DCM (0.15; p=0.15) and DCM (0.91 ± 0.34) was not significantly changed when compared to NF. However, the expression of Wnt-11 receptors was highly increased: Fzd-4 in ICM (6.25 ± 1.23; p<0.005) and in DCM (4.81 ± 0.82; p<0.005) as well Fzd-7 in ICM (4.48 ± 0.63; p<0.001) and in DCM (4.45 ± 0.76; p<0.001). The expression of Dvl-1 tended to be decreased in ICM (0.63 ± 0.15; p<0.15) and DCM (0.64 ± 0.29; p=0.17). The amplitude of Ca2+ transients (F/F)0, time to peak, and time to 50% decay (RT50) were not altered during 5 and 25 minutes incubation with Wnt-11 when compared to untreated control cells.

The expression of the Wnt-receptors, Fzd-4 and Fzd-7 is significantly increased indicating HFPEF with pulmonary congestion. Fibrosis was increased in LV from NXX. LV cardiomyocytes showed significantly prolonged time for early (50%) relaxation and decay of the Ca2+ transient. Time constant of the caffeine-induced Ca2+ transient (TAU) was significantly prolonged. However, a direct link between changes of nuclearplasmic Ca2+ handling and altered excitation-transcription coupling during the heart failure progression was not previously established. We thus characterized changes of nuclear Ca2+ handling and the activation of nuclear Ca2+-dependent transcription factors under low and high pacing frequencies at the early and late stage of hypertrophy in mouse model of pressure overload.

Ventricular cardiomyocytes were isolated 1 and 7 weeks after transverse aortic constriction (TAC) in adult wild-type mice. Subcellular [Ca2+]i transients were recorded in electrically stimulated CMs loaded with Fluo-4/AM. Phosphorylation levels of CaMKII and nuclear accumulation of HDAC4 were quantified by immunocyto staining.

During the early remodelling (i.e. 1 week after TAC intervention) - in contrast to diastolic [Ca2+]i in the cytoplasm - diastolic [Ca2+]i in the nucleus was already elevated at very low stimulation rate (0.5 Hz) as compared to the non-failing group, and than overproportionally increased with faster stimulation rates. In failing cardiomyocytes (7 weeks after TAC intervention), the changes in nucleoplasmic and cytoplasmic diastolic [Ca2+]i were qualitatively comparable, though the increase was more pronounced in the nuclear compartment. High pacing frequency caused significantly higher phosphorylation of CaMKII and corresponding HDAC4 translocation in cardiomyocytes from hypertrophic hearts compared to healthy controls, with the significantly higher increase in CaMKII phosphorylation in the nucleoplasmic compartment as compared to cytoplasm.

In conclusion, we found that the increased stimulation frequency led to a higher build-up of diastolic [Ca2+]i in cardiomyocytes from hypertrophied hearts, especially in the nucleoplasmic compartment, which may be involved in the dysregulation of Ca2+-dependent gene transcription and progression of adverse cardiac remodeling.