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Nuclear Ca homeostasis and mechanisms of remodeling in heart failure mediated atrial cardiomyopathy

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Introduction: Impaired left atrial function is highly prevalent in atrial remodeling and increases mortality in the setting of heart failure with preserved ejection fraction (HFpEF). We postulate that atrial remodeling is associated with atrial dysfunction related to altered Ca release and the interaction between cardiomyocytes and fibroblasts. In addition, we hypothesize that nuclear Ca homeostasis is altered in atrial cells during HFpEF and that nuclear Ca release is disproportionately susceptible during states of increased neuro-humoral signaling as it might be observed in HFpEF.

Methods: We used echocardiography, pressure-volume-loop invasive hemodynamic measurements and confocal line-scan imaging (Fluo-4 AM, 1Hz) as well as ratiometric microscopy (Fura-2). Measurements were performed in a metabolic syndrome model of HFpEF (ZSF-rats) at an age of 21 and 27 weeks. Ca transients (CaT) were recorded after treatment with conditioned medium of their respective cultured unstressed or stressed (stretch-induced activation; Flexercell system) fibroblasts isolated from WT and Ob. Tubular structures were measured using Di-8ANEPPS. Pico-Sirius Red stainings were used to quantify fibrosis. In addition, cardiomyocytes were exposed to Angiotensin II (Ang II) and CaT were studied.

Results: HFpEF animals showed preserved LVEF, an increased LVEDP, E/e' and left atrial (LA) size while LA function was impaired. In-vitro Ca release and contractile performance was augmented under baseline conditions during HFpEF, while SR Ca content was preserved and Ca leak increased. This augmentation of Ca release was related to an increased prevalence of tubular structures containing ryanodine receptors in the cell-center. Nuclear Ca release was unchanged in HFpEF under baseline conditions. Next, an activation of the neuro-humoral signaling cascade was mimicked in-vitro by addition of Ang II: It significantly increased total nuclear Ca as well as the ratio of total nuclear to total cytosolic Ca in HFpEF. This suggests that Ang II promoted active Ca release from nucleoplasmic Ca stores possibly via IP3 receptor mediated Ca release. Myocardial fibrosis in the upper atrium was increased in HFpEF. After treatment with supernatant from stretched fibroblasts, Ca time-to-peak and Ca removal were impaired and diastolic Ca was significantly increased in HFpEF cells indicating functional impairment.

Summary: Atrial remodeling in ZSF HFpEF is associated with atrial contractile dysfunction in vivo, indicating insufficient compensation related to increased fibrosis and fibroblast – cardiomyocyte interaction. Ang II reduced in vitro cytosolic CaT amplitudes and let to active nuclear Ca release in Ob but not in WT possibly affecting Ca dependent signaling cascades in HFpEF.