Effects of atrial fibrillation on ventricular remodeling in the human heart

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Atrial fibrillation (AF) is often found in patients with heart failure (HF). Clinical data indicated that the arrhythmic component of AF alone could contribute to left-ventricular (LV) dysfunction. However, the effects of non-tachycardic AF with arrhythmic excitation of the human LV, are unknown.

We investigated human LV myocardium from patients with sinus rhythm (SR) or normofrequent AF (mean EF>50%, matched clinical data, derived from septal resections during AVR). In histological analysis we detected no difference between SR (n=17 patients) and AF patients (n=18) regarding the amount and distribution of fibrosis. We isolated human LV cardiomyocytes (CM) and studied cellular Ca-handling (Fura-2). Systolic Ca-transient amplitude of LV CM was reduced in patients suffering from AF (n=8 AF patients vs. 11 SR), while diastolic Ca-levels and Ca-transient kinetics were not significantly changed. These results were confirmed in LV CM from non-failing donors (NF) with AF (n=4 AF patients vs. 8 SR). For the standardized investigation of a normofrequent arrhythmia, we simulated AF in vitro by using arrhythmic (60 bpm, 40% beat-to-beat variability) or rhythmic (60 bpm) field stimulation. Human LV CM from NF SR patients (n=8) showed an impaired Ca-transient amplitude after 24h arrhythmic culture pacing without changes in diastolic Ca and Ca-transient kinetics. For studying a model suitable for more standardized chronic pacing, we utilized human iPSC cardiomyocytes (iPSC-CM) from healthy donors (n=6). After 7 days, arrhythmically paced iPSC-CM exhibited a reduced systolic Ca-transient amplitude, a trend towards a prolonged Ca-elimination time and a reduced sarcoplasmic reticulum Ca-load. Confocal line-scans of arrhythmically paced cells (Fluo-4 AM) showed an increased diastolic Ca-leak from the sarcoplasmic reticulum, possibly underlying the reduced Ca-load. Coupled with the Ca changes, cytosolic Na was elevated after arrhythmia. We found an increased late INa, which could explain the detrimentally altered Ca/Na-interplay. Accordingly, Patch-clamp experiments revealed a prolonged action potential duration after arrhythmia. We further elucidated the underlying mechanisms of this electrophysiological remodeling by showing that oxidative stress (H2O2, LPO) is increased in the LV of patients suffering from AF (n=6 AF patients vs. 6 SR), which was associated with an enhanced NOX2/-4 activity. Consecutively, Ca2+/calmodulin-dependent protein kinase IIδ (CaMKII) was found to be more oxidized (CaMKII-Met281/282) in the LV of AF patients (n=7 AF patients vs. 7 SR) leading to an increased CaMKII activity, which adversely regulated EC-coupling protein phosphorylation including RyR2 hyperphosphorylation.

Normofrequent arrhythmia/AF impairs human ventricular EC-coupling via increased oxidative stress and enhanced CaMKII. Thus, this translational study provides the first mechanistic characterization and the potential negative impact of isolated AF on the human LV.