

Atrial Gene Transfer of CaMKII Inhibitor Decreases Atrial Fibrillation Burden

Introduction: Atrial Fibrillation (AF) is the most common arrhythmia in clinical practice, and cause of considerable morbidity and mortality. *In vitro* and small animal studies suggest a role of calcium/calmodulin-dependent protein kinase II (CaMKII) in the pathogenesis of AF. However, its effects in more complex situations, such as structural heart disease of large mammalian systems have not been yet established. We hypothesized that CaMKII mediates the maintenance of AF through structural remodeling of the atria.

Methods: Sustained AF was induced in ten Yorkshire pigs by atrial burst pacing for two weeks; ventricular activation was left unrestrained, leading rapidly to a tachycardiomyopathy and decompensated Heart Failure. At the time of device implantation, we randomized animals to receive either a specific CaMKII inhibitory protein (CaMKIIN) encoded within an Adenovirus vector or saline, via an epicardial atrial painting method. Animals were tested with baseline and sacrifice echocardiographical and electrophysiological studies, and post-sacrifice patch clamp, histology, and molecular analyses. Daily telemetry recordings were used to assess AF burden as the primary endpoint.

Results: Following initiation of pacing protocol, control animals developed sustained AF and HF within one week. CaMKIIN gene transfer significantly reduced AF burden, with the most prominent effect during days 4 to 12. CaMKIIN animals also had a significant improvement in left atrial ejection fraction, and a strong trend towards less atrial enlargement. Whole-cell recordings of isolated atrial myocytes revealed a mild prolongation in the action potential duration in the CaMKIIN group, and a variety of ion current changes, though none of them achieved statistical significance. On histological analysis, CaMKIIN animals had reduced atrial cell and nuclear hypertrophy. This was likely mediated by a reduction in total HDAC₄ and CaMKII-phosphorylated HDAC₄ levels compared to controls. Oxidized CaMKII levels were also significantly decreased in the CaMKIIN group, whereas total CaMKII and autophosphorylated CaMKII levels were similar in both groups. There was no difference in the degree of interstitial fibrosis.

Conclusions: Inhibition of CaMKII by adenoviral gene transfer significantly reduced the degree of AF burden, confirming our hypothesis that CaMKII mediates the maintenance of the arrhythmia. CaMKIIN animals had improved atrial contractile function and decreased atrial hypertrophy, likely through oxidized CaMKII and HDAC4 pathways. The degree of interstitial fibrosis or electrical remodeling was not significantly different than controls. Our findings not only shed light into the mechanisms of the arrhythmia, but they open the door for novel therapies for AF prevention.