Atrial remodeling in a murine model of hypertrophic cardiomyopathy: implications for atrial fibrillation

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Introduction: Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiac disease affecting 1 in 500 of the general population. Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia clinically presented in patients with HCM and a significant contributor to heart failure progression and embolic stroke deaths. It is unclear if the atria in patients with HCM demonstrate electrophysiological remodeling predisposing patients to AF.

Methods: We studied the Gly203Ser cardiac troponin-I (TnI) transgenic line of mice that fully develops hallmarks of HCM by 21 weeks of age. Tail tip genotyping was used to identify transgenic mice (TG) from their wild-type (WT) counterparts. Upon reaching 30 or >50 weeks of age, TG and WT mice were anesthetized (n=6 each group) and the left atria (LA), right atria (RA), ventricles were excised and the wet weights measured. Ventricles were sliced midway between the base and apex and the LV wall thickness was measured *via* ImageJ. The LA was placed on a custom-made micro-electrode array (25 electrodes with 0.5mm inter-electrode spacing) and an intracellular microelectrode inserted to simultaneously measure action potential duration (APD). Effective refractory period (ERP) was measured using standard extra-stimulus pacing. Conduction velocity (CV) and conduction heterogeneity index (CHI) were subsequently analysed offline. Atrial tissue was stored in formalin for histological processing.

Results: LA mass and LV wall thickness was significantly greater in TG mice compared to controls. Mice heart rate and blood pressure were similar between anesthetized TG and WT mice. APD20, 50, and 90 were significantly reduced in TG mice across all paced cycle lengths ($P<0.001$). ERP and CV were not significantly different between TG and WT mice at 30 weeks. In the older TG mice, a significant increase in ERP and decrease in CV was observed (both $P<0.001$). CHI was significantly greater in TG mice compared to controls at both ages (both $P<0.001$). Atrial myocyte hypertrophy was observed in TG mice across both age groups as compared to age-matched controls.

Conclusions: Mice with the TnI gene mutation develop atrial hypertrophy as evident by greater LA mass and myocyte hypertrophy. TG mice also demonstrate age-related differences in conduction parameters of the LA. This electrophysiological remodeling may in part explain the increased susceptibility to AF in patients with HCM with increased age and may have implications for therapies in this cohort.