Abstract: P3483
Diet governs metabolic and electrical properties of the atrial myocardium in mice

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Topic(s):
Basic Science - Cardiac Diseases: Arrhythmias

Citation:
European Heart Journal (2019) 40 (Supplement), 2098

Background: Obesity is associated with an increased risk of atrial fibrillation. This epidemiologic observation may not only be due to shared co-morbidities but also from direct impacts of metabolic disorders on myocardium. Here, we examined the impact of high fat diet (HFD) induced obesity on atrial properties in mice.

Methods: Eight weeks old C57Bl/6J mice were subjected to 2 or 4 months of HFD (60% fat) or normal diet (ND, 4% fat). Rapid burst atrial pacing were delivered using a trans-esophageal probe to induced AF in anesthetized animals. Action potential (AP) were recorded in left atrial trabeculae using glass microelectrode technique. Potassium currents were recorded in isolated atrial myocytes using the whole cell or perforated patch clamp configurations. Metabolomic and lipidomic analysis were performed on whole left atria. Mitochondrial respiration was studied in situ in saponin-permeabilized atrial muscle fibres using a Clarke electrode and oxygen consumption was measured after successive addition of ADP (2 mM), malate (4 mM), palmitoyl-CoA and carnitine (pCoA-Ca) (100 μM and 2 mM), pyruvate (1 mM), glutamate (10 mM), succinate (15 mM), amytal (1 mM) and tetramethyl-paraphenylenediamine (TMPD)/ascorbate (0.5/0.5 mM).

Results: HFD mice showed a higher atrial vulnerability to AF as indicated by longer AF episodes compared to ND mice. APs were shorter in HFD versus ND mice (AP duration measured at 90% of repolarization: 47.9±2.4 msec in HFD vs 58.2±1.4 msec in ND, P<0.001 after 2 months of HFD) and more sensitive to the K-ATP channel blocker, glibenclamide. In perforated but not whole cell, patch clamped atrial myocytes, the K-ATP component of the potassium current was enhanced in HFD mice (at +70 mV: 0.41±0.12 pA/pF in HFD vs 0.13±0.08 pA/pF in ND, P<0.05). Metabolomic analysis indicated an increased consumption of free fatty acid by the beta-oxidation and an accumulation of long chain fatty acid. Although the mitochondrial respiration measurements showed a trend towards a lower complex IV-driven respiration in HFD mice, no significant difference between ND and HFD was noted regarding complex I and complex II-driven respiration. However, the ability of fatty acids (pCoA-Ca) to support mitochondrial respiration was higher in HFD.

Conclusions: High fat diet induces a shift from carbon hydrate to a beta oxidation of the atrial myocardium metabolism together with an enhanced use of fatty acids by mitochondria. These metabolic changes could result in an enhanced activity of K-ATP channels and AP shortening that might contribute to AF vulnerability in this clinical setting.