**EPICARDIAL ADIPOSE TISSUE ASSOCIATES WITH ELECTRICAL, STRUCTURAL AND MOLECULAR ATRIAL REMODELLING IN HUMANS: DEFINING THE SUBSTRATE FOR ATRIAL FIBRILLATION IN OBESITY.**

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**Introduction:** Epicardial adipose tissue (EAT) has emerged as an important driver of atrial fibrillation (AF) in obesity. While limited animal data exists, its impact on the human substrate remains poorly understood. We aimed to characterize the association of EAT content with the human atrial substrate at electrophysiologic, histologic and molecular levels.

**Methods:** We recruited patients without AF undergoing coronary artery bypass surgery. Following computed tomography to quantify anterior right atrial EAT volumes, we performed intra-operative high density epicardial mapping of the anterior RA (pacing @600ms and 300ms). The right atrial appendage including the mapped region was processed for Western blot analysis of connexin (Cx) 43/40 expression, or sectioned and stained with picrosirius red/oil red O for fibrosis/adipose analysis. Sections were classified (Grade I-III) based on the degree of adipose infiltration.

**Result:** Nineteen patients (male 78%, age 64±6, BMI 30±7) with median anterior RA EAT volumes of 3.10ml (2.50-5.80) were recruited. Higher EAT volumes associated with longer plaque activation times (600ms r=0.49 p=0.04, 300ms r=0.49 p=0.03), slower conduction velocities (600ms r=-0.46 p<0.05, 300ms r=-0.49 p=0.04) and greater proportion fractionated signals (600ms r=0.69 p=0.001, 300ms r=0.66 p=0.003). At histologic and molecular levels, EAT content correlated with more extensive fibrosis (r=0.70 p<0.001), greater Cx40 expression (r=0.45 p=0.05) and sarcolemmal lateralisation (p<0.05). A strong correlation between fibrosis content and Cx40 (r=0.55 p=0.02) expression was observed. Atrial tissue infiltration by EAT was heterogenous; higher grades of infiltration associated with greater conduction heterogeneity (Grade I vs II/III @ 600ms and 300ms p<0.03).

**Conclusion:** EAT content associates with atrial remodelling at electrophysiologic, histologic and molecular levels, characterised by slowed/distorted atrial conduction, atrial fibrosis, gap junction remodelling and adipose infiltration. These insights identify a putative mechanism for AF in obesity and may facilitate development of therapies that target EAT and its impact on the atrial substrate.