**Weight fluctuation induces atrial substrate by fibro-fatty depositions, myolysis, and residual electro-structural remodelling in an ovine model**

**Introduction**: Obesity-mediated epicardial adipose tissue (EAT) expansion drives the deposition of fibro-fatty infiltrates, which form the unique substrate for atrial fibrillation (AF). The LEGACY study showed the benefits of weight loss but an attenuated response with weight fluctuation. How fluxes in weight impacts the atrial substrate remains unknown. Here, we investigated cardiac adiposity and the atrial substrate due to weight fluctuation.

**Methods**: We studied 24 sheep in 3 equal groups over 80 weeks: 1. Obesity was induced by high calorie diet fed ad libitum; 2. Weight fluctuation by 20-week cycle of weight gain/loss; and 3. Lean controls maintained at baseline weight. All sheep underwent: daily weight measurement; haemodynamic and imaging assessments (CMRI & DEXA); electrophysiological studies; and histological, and structural analysis.

**Result**: The Table shows the group differences. Compared to reference controls, obesity demonstrated: increased atrial volume and pressure, abnormal atrial electrical properties, expanded EAT and ensuing fibro-fatty infiltrations, and myolysis of myocytes. Despite comparable weight and EAT with controls, weight fluctuation resulted in extensive and severe fibro-fatty infiltrations, and twofold greater myolysis that persisted. More importantly, fibro-fatty infiltrates strongly correlated with increased atrial volume and pressure; fractionated electrograms ($r=0.71$, $p<0.001$) and conduction slowing ($r=-0.59$, $p=0.006$). Similarly, atrial myolysis exhibited significant correlations with atrial enlargement and haemodynamics, and electrical substrates ($p<0.05$ for all).

**Conclusion**: Despite final weight loss and non-expanded epicardial fat depot, weight fluctuation demonstrates residual electro-structural, fibro-fatty deposition, and abnormal contractile substrates, similar to stable chronic obesity, but to a less severe extent. This may indicate an important mechanism for atrial fibrillation in subjects with weight fluctuation.