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**Epicardial progenitors are source of myofibroblasts that contribute to fibro-fatty infiltration of atrial subepicardium**

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**Background & Aims.** Atrial fibrillation (AF), the most frequent cardiac arrhythmia, is often associated with a true atrial cardiomyopathy composed, notably, of fibro-fatty infiltrations of the subepicardium that favor atrial electrical heterogeneity. A balance between adipose tissue (AT) expansion and fibrosis appears to regulate fibro-fatty infiltration of the epicardial area. We previously showed that progenitor cells resident in the atrial epicardial layer (EPDCs) can be a source of adipocyte. Here we examined the role of epicardial layer in fibrosis of the atrial subepicardium.

**Methods.** Specimen of human right atrial obtained during cardiac surgery were used for histological analysis (n=95). Clinical and histological data were analyzed using proportional hazards models to examine associations between AF and histological risk scores, added to a model adjusted for classic risk factors. Model of ischemic heart failure (HF) atrial dilation and AF vulnerability was created in rats and in lineage tracing Wt-1-Cre-Rosa-tdT+/+ mice (n=8). Clinical phenotypes were obtained using echocardiography and electrocardiogram recordings.

**Results.** Thickness of atrial epicardial correlated with adipose tissue accumulation (r²=0.492, p<0.001) and varied with clinical history. For instance, it was associated with an history of AF (AUC 0.78, p=0.0441), HF (AUC=0.706, p=0.057) and valve mitral regurgitation with atrial dilation (AUC=0.785, p=0.004). In rat too, HF and atrial remodeling were associated with thick epicardial layer and subepicardial fibrosis. In human, thin epicardial layer, tightly associated with adipose tissue depots, was composed of a monolayer of cells expressing the epicardial progenitor protein WT1+ (EPDCs). Thick epicardial layer was composed mainly of extracellular matrix (ECM) (collagen-1+), few cells expressing mesenchymal and myofibroblast markers (FSP1+, PDGFRα+, aSMA+) were detect in the matrix. Some of them positive for PDGFRα+ and aSMA+, expressed WT-1 marker, suggesting an epicardial origin. This was supported by the observation of WT1-tomato positive cells expressing PDGFRα+, aSMA+ in the dilated atrial of WT1-tdt+ mice in HF.

**Conclusion.** Epicardial layer is an important component of the atrial cardiomyopathy and EPDCs can be a source of myofibroblast contributing to fibro-fatty infiltrations of the subepicardium. Mechanisms regulating the fate of EPDCs and their differentiation into myofibroblast or adipocyte will be discussed.