Metformin breaks the vicious cycle between atrial fibrillation and epicardial adipose tissue remodeling

**Introduction**: Epicardial adipose tissue (EAT) remodeling is important for the pathogenesis of atrial fibrillation (AF). We investigated if metformin (MET) prevents AF-dependent EAT remodeling and AF vulnerability in dogs.

**Methods**: Eighteen male beagle dogs were randomly divided into three groups: (i) sham-operated (normal diet without pacing, \(n=6\)), (ii) RAP (Rapid atrial pacing, \(n=6\)), and (iii) RAP+MET (RAP with MET). AF model was induced by rapid atrial pacing (RAP) at 400 bpm for 4 weeks with a programmable pacemaker. Daily oral administration of MET (100 mg/kg) was initiated 1 week before surgery and continued throughout the study period. The electrophysiological parameters including effective refractory period (ERP), window of vulnerability induced window (WOV) and AF duration, AF inducibility were measured before and after 6 weeks RAP. The content of ROS, inflammatory factor APN and related signaling pathway protein in LA and EAT were detected. To detect the effect of MET on the interactions between HL-1 atrial myocytes and 3T3-L1 mature adipocytes, HL-1 were indirectly co-cultured with LPS-treated 3T3-L1 via an exchange medium.

**Result**: In vivo, MET attenuated the RAP-induced decrease in effective refractory periods (ERP) and increase in ERP dispersion, cumulative window of vulnerability, AF inducibility, and AF duration. RAP increased ROS production and NF-κB phosphorylation, upregulated IL-6, TNF-α, and TGF-β1 levels in LA and EAT, decreased PPARγ and adiponectin (APN) expression in EAT, and were accompanied by atrial fibrosis and adipose infiltration. MET was shown to reverse the alterations described above. In vitro, LPS stimulated 3T3-L1 adipocytes inflammatory factor expression and decreased APN expression. Indirect coculture HL-1 cells with LPS-stimulated 3T3-L1 conditioned medium (CM) significantly increased inflammatory response and decreased SERCA2a and p-PLN expression, while LPS+MET CM and APN treatment alleviated the inflammatory factor expression and SR Ca2+ handling dysfunction.

**Conclusion**: MET attenuated RAP-induced increase in AF vulnerability and remodeling of atria and EAT adipokine production profiles and APN may play a key role in MET breaking the vicious “AF begets AF” cycle.