Abstract: P520
The metabolic modulator trimetazidine inhibits AF-induced atrial structural remodelling

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Introduction: Atrial fibrillation (AF) is a progressive disease, perpetuated by remodeling of atrial structure. We have recently shown that AF leads to metabolic derangement in first minutes to weeks of AF. Trimetazidine (TMZ) has pleiotropic effects, including improved oxygen efficiency, decreased ROS production and mitochondrial protection.

Purpose: We have investigated whether improving atrial energy production and inhibiting ROS production with TMZ treatment inhibits AF stabilization and AF-induced atrial remodeling.

Methods: Dutch female white milk goats were instrumented with pericardial electrodes and AF was maintained by burst pacing for 16 weeks. Eight goats were treated with 20mg/kg of TMZ two times per day from 7 days before AF initiation until sacrifice, while 10 untreated animals with AF were used as controls. Ten sham animals received the same instrumentation, but AF was never induced.

Results: TMZ treatment abolished AF-induced increase in left atrial (LA) resting superoxide production that mainly originated from mitochondria (LA Resting O₂⁻ 47.1±2.8 vs. 79.7±7.4 vs. 40.0±6.5 RLU/sec/mg of protein, p<0.05; Rotenone stimulated 181.0±27.9 vs. 309.0±24.0 vs. 173.30±28.77 RLU/sec/mg of protein, P<0.05; for sham, control AF and TMZ treated AF respectively). However, the markers of oxidative stress (LA GSH/GSSG ratio: 50.8±9.3 vs. 66.8±6.9 vs. 74.9±16.0, p=n.s.) and oxidative damage in the left atrium (LA Malondialdehyde (MDA): 9.6±1.3 vs. 9.2±0.9 vs. 8.0±0.7 pmol of MDA per mg heart tissue, p=n.s.) were not affected either in untreated or treated animals. This suggests increased ROS neutralizing capacity, which was indeed reflected in increased levels of the glutathione system (536±140 vs. 1034±91 vs. 1130±178 pmol GSH+GSSG per mg heart tissue, p<0.05).

TMZ treatment did not affect early AF stabilization (Time to 24h AF episode 74.1±9.1 vs. 79.7±28.9h; p=ns), but it inhibited structural remodeling, as reflected by inhibited atrial cardiomyocyte hypertrophy (cardiomyocyte diameter:11.4±0.2 vs. 13.3±0.2 vs. 12.7±0.3μm; p<0.05), tendency towards decreased cell to cell distance (3.2±0.1 vs. 3.5±0.1 vs. 3.3±0.1μm, p<0.05;) and by preserved mitochondrial structure (single mitochondrial area: 124.5± 6.7 vs. 92.3±6.7 vs. 119.5±6.7 pixels; p<0.05;).

Conclusion: TMZ did not affect early AF stabilization, but did reduce AF-induced ROS production and attenuated several hallmarks of structural remodeling. Adjunctive therapy with TMZ may be useful in preserving atrial structure and function during AF.
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