Acute oestradiol slows conduction and prolongs action potential duration in the left atrium, but not in cardiomyocyte cultures

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Background: There is emerging evidence for a link between pericardial adipose content and atrial fibrillation risk, although the underlying mechanisms are poorly understood. We have shown exogenous oestradiol increases atrial arrhythmia vulnerability – consistent with evidence of increased atrial fibrillation risk in menopausal women given oestrogen-only hormone replacement. We have also demonstrated that pericardial adipose expresses aromatase (catalyses androgen-oestrogen conversion), and that total aromatase capacity of pericardial adipose correlates with atrial arrhythmia vulnerability. We hypothesize that pericardial adipose-derived oestrogens may increase atrial arrhythmias by prolonging repolarization and slowing conduction.

Aim: The aim of this study was to determine how acute administration of oestrogens modulates cardiac conduction properties in spontaneously beating cardiomyocyte monolayers and the intact left atrium (LA).

Methods: Spontaneously beating monolayers of neonatal rat ventricular myocytes (NRVMs) seeded onto microelectrode arrays (59 electrodes, 200 μm spacing) were exposed to increasing concentrations of oestradiol (in nM: 0, 0.1, 1, 10 and 100). Field potentials and local activation times were used to generate conduction maps in Cardio2D+ software (MultiChannel Systems). Adult male mouse LA were stained with potentiometric dye (Di-4-ANEPPS), electrically paced and superfused with increasing concentrations of oestradiol (in nM: 0, 1 and 100). Optical action potentials were recorded using a high sampling CMOS camera. Conduction velocity and action potential duration at 70% repolarization (APD_{70}) were analysed using custom-made MATLAB codes.

Results: Oestradiol had no effect on NRVM electrophysiology, including: spontaneous beating rate (100 nM oestradiol *vs* vehicle: 77 ± 8 bpm *vs* 69 ± 6 bpm), field potential duration (204.4 ± 20.7 ms *vs* 182.4 ± 13.3 ms) and conduction velocity (20.1 ± 1.2 cm·s^{-1} *vs* 18.5 ± 2.4 cm·s^{-1}; in all cases: P = ns; $n_{oestradiol}$ = 5, $n_{vehicle}$ = 3). In isolated LA, 100 nM oestradiol caused a significant prolongation in APD_{70} *vs* vehicle (ΔAPD_{70}: 5.8 ± 0.9 ms *vs* 1.6 ± 1.6 ms; P = 0.037; $n_{oestradiol}$ = 6-8, $n_{vehicle}$ = 4-5) with a trend for reduced conduction velocity (Δconduction velocity: -13.5 ± 3.6 cm·s^{-1} *vs* -3.1 ± 2.0 cm·s^{-1}; P = 0.073). This reduction in conduction velocity was significant in the presence of 1 nM oestradiol (Δconduction velocity: -9.2 ± 1.8 cm·s^{-1} *vs* 1.1 ± 2.1 cm·s^{-1}; P = 0.006).

Conclusions: Oestradiol had no effect on NRVM electrophysiology, but caused APD prolongation and conduction slowing in the intact adult mouse LA. The lack of effect in NRVM may be partly due to downregulation of oestrogen receptors in non-oestrogenic culture conditions. APD prolongation in the mouse LA is consistent with data from other studies in both single cardiomyocytes and human ECGs, and is likely facilitated through I_{Kr}-mediated delayed repolarization. Oestradiol-induced conduction slowing may contribute to greater atrial arrhythmia vulnerability. Further studies will determine whether locally synthesised oestrogens from pericardial adipose exert paracrine actions on cardiomyocytes to increase conduction heterogeneity and reentrant arrhythmias.