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Male and female sex are associated with different derangements of the intracellular calcium homeostasis in atrial fibrillation

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Background: Atrial fibrillation (AF) has been associated with alterations in the intracellular calcium homeostasis in human atrial myocytes, but little is known about the potential influence of gender.
Purpose: We here aimed to address how gender affects the intracellular calcium homeostasis in human atrial myocytes from patients with and without atrial fibrillation.
Methods: Atrial myocytes from 203 male and 83 female patients undergoing cardiac surgery were analyzed to identify independent effects of cardiovascular risk factors, underlying disease and pharmacological treatments on intracellular calcium homeostasis using a multivariate linear regression model. Calcium currents and membrane potentials were measured with patch-clamp technique. Spontaneous calcium release was detected with confocal calcium imaging, and protein expression was assessed using immunoblotting.
Results: Multivariate regression analysis revealed gender-specific derangements of calcium homeostasis in patients with AF as compared to those free of AF. For L-type calcium current (ICa) the density was significantly reduced in males (from -2.3±0.2 to -1.4±0.3 pA/pF, p=0.001) but not in females (from -2.6±0.3 to -2.0±0.4 pA/pF, p=0.07). Opposite to this, the incidence of transient inward currents (ITi) induced by spontaneous calcium release increased from 0.9±0.4 to 2.5±0.6/min in females with AF (p=0.004) but not in males with AF (from 0.2±0.4 to 0.6±0.6/min, p=0.4). Similarly, spontaneous membrane depolarizations were more frequent in females with AF (4.6±1.4 vs 1.2±0.4/min, p=0.006) but not in males with AF (2.4±0.5 vs. 1.5±0.4/min, p=0.2). Mechanistic analysis revealed that females with AF had a higher calcium spark site density than those without AF (9.8±1.8 vs. 2.2±1.9/μm^2, p=0.006) while the presence of AF did not change the sparks site density significantly in males (6.3±1.8 vs. 3.9±1.9 μm^2, p=0.4). These changes in spark density and properties favor the fusion of sparks into calcium waves, triggering electrogenic calcium extrusion and spontaneous membrane depolarizations in females but not in males. The differential increase in spontaneous calcium release in females with AF was not due to higher SR calcium loading, sarcoplasmic endoplasmic reticulum calcium (SERCA) ATPase expression or phospholamban (PLB) phosphorylation, but could be caused by a higher RyR2 phosphorylation at ser2808 in women with than without AF (0.78±0.11 vs. 0.37±0.04, p=0.03).
Conclusion: Atrial fibrillation is associated with an increase in the incidence of spontaneous SR calcium release-induced electrical activity in women only, while the ICa density is differentially depressed in males with AF. These findings suggest a potentially greater efficiency of drugs targeting SR calcium homeostasis in females with AF and L-type calcium channels in males with this arrhythmia.
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Estrogen suppresses mRNA expression of fibrosis, apoptosis and hypoxia markers in the left ventricle ovariectomized mice - A mouse model of human menopause

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Introduction: Menopause is associated with increased cardiovascular morbidity and mortality. Cardiac hypertrophy is an independent risk factor for cardiovascular disease (CVD), and is more prevalent in post compared to pre-menopausal women and age-matched men. Cardiac fibrosis is associated with increased left ventricular filling pressures and the development of heart failure. The mechanisms by which estrogen withdrawal is associated with increased cardiovascular risk are not completely understood.
Purpose: To test the effect of systemic estradiol (E2) administration on markers of hypertrophy, fibrosis and apoptosis in the left ventricle (LV) of female mice that underwent ovariectomy (OVX).
Methods: Seven groups of 9-week-old C57BL/6 female mice (n=10 mice/group) were subjected to OVX or SHAM operation. Two groups (SHAM and OVX) were sacrificed one week post operation. The other groups were left untreated for 6 weeks when additional two groups (SHAM and OVX) were sacrificed. In the remaining groups daily 17-β-estradiol (E2) (10μg/kg) or a vehicle was administered subcutaneously for 6 weeks to OVX mice. Mice were sacrificed 12 weeks post operation. Upon sacrifice mRNA was extracted from the left ventricle (LV) apex. Gene expression was determined by SYBR Green Based quantitative Real Time PCR and was normalized to GAPDH.
Results: OVX mice had a dramatic early increase in body weight which was already noticed 2 weeks post operatively and continued until the end of the study. Interestingly, treatment with 17-β-estradiol did not abolish weight gain in OVX mice. OVX was associated with a statistically significantly increased expression of the fibrosis markers: Col1α1 (2.5 fold), Col3α1 (4.5 fold), Timp1 (2 fold) and Tgfβ1 (1.5 fold), the hypoxia marker Hif1α (2 fold) and the apoptosis marker FASL (2 fold), which was already observed one week postoperatively. A similar change in gene expression profile was noted six week postoperatively in OVX compared to SHAM mice, however the differences in the fibrosis markers between OVX and SHAM mice were smaller: Col1α1 (1.5 fold), Col3α1 (1.6 fold), Hif1α (1.3 fold), while the hypertrophy markers ANF (2.2 fold, p=0.07) and Myh7 (1.9 fold, p=0.0565) were increased in OVX mice at this time point. Strikingly, E2 administration significantly reduced the expression of fibrosis markers: Col1α1 (3.3 fold), Col3α1 (5.5 fold), Tgfβ1 (1.5 fold), Timp1 (1.6 fold, p=0.1) and Ctgf (2 fold,), the hypoxia markers Vegf-A (2.5 fold), Hif1α (1.5 fold, p=0.06), and the apoptosis marker FASL (4 fold).
Conclusions: Estrogen treatment suppresses the expression of fibrosis, hypoxia and apoptosis markers in the LV of OVX mice. These findings may partially explain the high incidence of heart failure with preserved ejection fraction in postmenopausal women, and may provide therapeutic targets to prevent heart failure.
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ABSTRACT WITHDRAWN

BEST POSTERS IN DEVICE THERAPY FOR HYPERTENSION.

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Biomarkers for prediction of target organ damage in hypertension

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Purpose: Hypertension is associated with several circulatory biomarkers and tar-