PITX2 overexpression leads to atrial electrical remodeling linked to atrial fibrillation

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Although functional analysis has shown that electrical remodelling in Atrial fibrillation (AF) patients is related to PITX2 overexpression, this link between PITX2 overexpression and the likelihood of atrial arrhythmias remains to be demonstrated directly. AF patients have been reported to exhibit the slow delayed rectifier potassium current (I_{Ks}) increase and the L-type calcium current (I_{CaL}) reduction, but failed to show alterations in action potential (AP) at the cellular level and cardiac dynamics at the tissue level. Consequently, the mechanisms by which altered I_{Ks} and I_{CaL} caused by PITX2 overexpression promote and perpetuate AF have not yet been elucidated. Therefore, utilizing computer modelling, this study was to quantify the pro-arrhythmogenic effects of PITX2 overexpression in the human atrium at cell and tissue levels. In simulations, Courtemanche *et al.*'s model of human atrial cell AP was modified to incorporate experimental data on changes of I_{Ks} and I_{CaL} induced by PITX2 overexpression. The cell models for normal and AF type ionic currents (I_{Ks} and I_{CaL}) were incorporated into the homogeneous multicellular 2D tissue model. Effects of electrical remodelling induced by PITX2 overexpression were quantified on ionic currents, AP profile and AP duration (APD). Temporal and spatial vulnerabilities of atrial tissue to genesis of re-entry were computed. Dynamic behaviours of re-entrant excitation waves in the 2D model were characterized. It was shown that the PITX2 overexpression abbreviated atrial APD. It reduced markedly the minimal substrate size necessary for sustaining re-entry (increasing the tissue spatial vulnerability). In the 2D model, the PITX2 overexpression also stabilized and accelerated re-entrant excitation waves, leading to rapid and sustained re-entry. In conclusion, increased I_{Ks} and reduced I_{CaL} due to the PITX2 overexpression increases atrial susceptibility to arrhythmia due to increased tissue vulnerability, shortened APD and abbreviated wavelength, which, in combination, facilitate initiation and maintenance of re-entrant excitation waves.