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Remodeling of atrial action potential duration and atrial chamber deformation: a potential link in the development of atrial fibrillation?

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Topic(s):
Basic Science - Cardiac Diseases: Arrhythmias

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S120

Electrical remodeling is a major determinant of the atrial fibrillation (AF) substrate associated or not to chronic heart disease. Action potential (AP) shortening plays a key role and results from the drastic reduction of the calcium current. Differently, repolarizing potassium currents are increased (the inward rectifier current, IK1), reduced (the transient outward current, Ito), or moderately altered (the ultra-rapid delayed rectifier potassium current, Ikur). This evidence and the atrial selective expression of IKur/Kv1.5 point to this channel as a potential antiarrhythmic target for AF. Interestingly, experimental evidence suggest that remodeling of atrial AP and IKur/Kv1.5 expression may be linked to atrial dilation, event that may precipitate or precede AF. In the human setting such a link is presently unexplored.

To address the specific role of Ikur in AP remodeling, we used F17727, a highly specific and open channel blocker of IKur/Kv1.5 (IC50=1.5µM) over the other major cardiac currents with the exception of Kv4.3 (61% inhibition at 10µM). Efficacy of F17727 in the human setting was tested in atrial myocytes isolated from patients in chronic AF and in sinus rhythm (SR) undergoing corrective cardiac surgery. AP recordings were performed using the perforated patch-clamp technique at different pacing rates (0.5, 1, and 2 Hz). At all rates, 10µM F17727 prolonged AP duration (APD), an effect, which was significantly more pronounced in the AF than in SR group. At 1 Hz, APD measured at 90% of repolarization was prolonged by 207.8±24.1 and 79.3±54.7ms in AF and SR group, respectively (n=5-6, p<0.05). AP amplitude and resting diastolic potential were not modified. To address the association between atrial deformation and AP remodeling, in a selected group of patients with or without chronic AF, speckle tracking echocardiography was performed prior to cardiac surgery. Analysis gave a range of mechanical parameters, namely atrial mechanical dispersion and global peak atrial longitudinal strain (PALS), both related to atrial deformation. For each patient, AP parameters were measured from single atrial myocytes dissociated from samples discarded during cardiac surgery. Interestingly, both mechanical dispersion and global PALS resulted linearly related with AP duration evaluated at different values of repolarization.

In conclusion, Ikur selective blockade has potential antiarrhythmic properties on the atrial AP of AF and SR patients, which is more pronounced in AF, suggesting a gain of function of Ikur in AF. Atrial AP duration of AF and SR patients is linearly related with atrial deformation, suggesting a potential link between atrial electrical remodeling and chamber deformation. Further investigations are necessary to corroborate the predictive value of speckle tracking echography for atrial arrhythmogenic remodeling.