

## REMODELING OF ATRIAL REPOLARIZATION AND ATRIAL CHAMBER DEFORMATION: A POTENTIAL LINK IN THE DEVELOPMENT OF ATRIAL FIBRILLATION?

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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 moderately increased or reduced, such as the inward rectifier current,  $I_{K1}$ , or the transient outward current,  $I_{to}$ , respectively, or moderately altered, mainly the ultra-rapid delayed rectifier potassium current,  $I_{Kur}$ . These results and the atrial selective expression of  $Kv1.5/I_{Kur}$ , point to this channel as a potential antiarrhythmic target. Additionally, emerging experimental evidence suggest that remodeling of atrial repolarization and  $Kv1.5/I_{Kur}$  expression may be linked to atrial dilation, a phenomenon that may precede the development of arrhythmias. In the human setting such a link is presently unexplored.

To address the specific role of  $I_{Kur}$  in electrical remodeling, we used F17727 as a highly specific and open channel blocker of  $Kv1.5/I_{Kur}$  ( $IC_{50}=1.5\mu M$ ) over the other major cardiac current including  $Nav1.5$ ,  $hERG$ ,  $KVLQT1/mink$  ( $IC_{50} > 10\mu M$ ) with the exception of  $Kv4.3$  (61% inhibition at  $10\mu M$ ). Efficacy of F17727 in the human setting was tested in right 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,  $10\mu M$  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  $207.8 \pm 24.1$  and  $79.3 \pm 54.7$  ms 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 remodeling of repolarization, in a selected group of patients with or without chronic atrial fibrillation, speckle tracking echocardiography was performed prior to corrective 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 patients, AP parameters were measured from single atrial myocytes dissociated from samples discarded after cardiac surgery. Interestingly, both mechanical dispersion and global PALS resulted linearly related with AP duration evaluated at different values of repolarization.

In conclusion,  $I_{Kur}$  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  $I_{Kur}$  mediated repolarization 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 test the predictive value of speckle tracking echography for atrial arrhythmogenic remodeling.

