Substrate for arrhythmias in acute atrial dilatation

Introduction. Atrial fibrillation (AF) is commonly associated with atrial dilatation caused by acute pressure or volume overload. Mechanisms that create a myocardial substrate to promote AF after acute atrial stretch may involve gap junction conductivity as well as changes of sarcolemmal channels properties. Purpose. Here, we dissect the mechanisms of acute stretch-related changes versus those occurring as part of the long-term remodeling process in rat models of acute and chronic atrial dilatation. Methods. Spontaneous hypertensive rats (SHR) with chronic atrial dilation were compared to normotensive rats (CTRL) and to rats with acute biatrial dilation (ABD) obtained with atrial balloons (inserted into both atria and inflated with controlled pressure after baseline recording). Briefly, the hearts were perfused on a Langendorff’s apparatus and then the ventricles were excised just below the atrio-ventricular junction. To maximize atrial perfusion and staining main coronary ventricular branches were cauterized. Atria were stained with a bolus injection of a voltage-sensitive dye (di-4-ANBDQPO). A wide-field mesoscope was used to optically map action potential propagation of Langendorff’s perfused-atria and to test AF vulnerability. Results. Compared to CTRL, the occurrence of AF episodes was increased in ABD and SHR. AF episodes exhibited a stable reentry pattern characterized by similar origin and propagation on beat-to-beat basis in CTRL and ABD. The arrhythmias were sustained by multiple coexisting reentrant circuits in SHR. Action potential duration (APD) was unchanged in ABD but prolonged in SHR. Conduction velocity (CV) was reduced in both, SHR and ABD. Low-dose caffeine (2.5 µM) was used to increase diastolic calcium levels, that are expected to decrease gap-junction conductivity. In CTRL rats under caffeine we found no changes of APD but a significant reduction of CV. In this condition, when atrial dilatation was applied we observed no changes of APD and a drop of CV that was quantitatively similar to the one observed in untreated animals. We also found that caffeine systematically increase the occurrence of arrhythmias in CTRL and ABD rats. The effect of a pharmacological compound used for treat acute AF (Ranolazine) in relation to anti-arrhythmic response was also investigated. We found that in CTRL acute application of Ranolazine (10 µM) causes a prolongation of APD with no changes of CV. In this condition, acute dilatation restores APD and decrease CV with the similar extent found in untreated rat. Finally, we found that Ranolozine markedly reduce the occurrence of arrhythmias in ABD rats. Conclusions. A reduction of gap-junction permeability (trough increased diastolic calcium) does not reduce the drop of conduction velocity caused by acute atrial dilatation. Ranolazine, by changing APD rather than CV, prevents the occurrence of atrial arrhythmias in acutely dilated atria.