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SK channels contribution to ventricular electrophysiology in heart failure patients

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Introduction: Heart failure (HF) is characterized by deterioration of the electrical and contractile function of the heart due to structural and functional remodelling, leading to development of arrhythmias and increased sudden cardiac death risk. SK channels are a type of calcium-activated potassium channels that do not play a relevant role in normal ventricular electrophysiology. However, it has been hypothesized that these channels become more relevant in pathologies such as HF. Nontheless, their role in human ventricular electrophysiology is not fully characterized.

Purpose: We aimed to determine the presence and function of SK channels in the ventricle of HF patients by characterizing action potential duration (APD) changes produced by modulation of SK channels in ventricular tissue slices.

Methods: Left ventricular transmural biopsies and papillary muscles were taken from 9 HF patients. Control tissues (without ventricular remodelling) were taken from an area not affected by ischemic disease from 3 patients with ischemic cardiomyopathy. Samples from the mid-myocardium (from biopsies) and endocardium (from papillary muscles) were evaluated separately. All patients gave written informed consent prior to surgery and their inclusion in the study, which complied with the principles of the declaration of Helsinki and was approved by the local ethics committee (PI17/0023). Tissue slices of 350μm thick were produced in a high precision vibratome and maintained in cold, pre-oxygenated Tyrode's buffer. Tissue slices were optically mapped after staining with RH237. APDs were measured at different stimulation frequencies from 0.5 to 3 Hz, at baseline and after addition of SKA-31 100μM, a selective activator of SK channels. The notation n/N is used to denote n tissue slices from N samples. Wilcoxon test for paired samples was used for statistical evaluation. A p-value <0.05 was considered as statistically significant.

Results: SKA-31 shortened the APD at all frequencies in HF patients (n/N=32/9), whereas no significant change was observed in the control group (n/N=11/3). In the endocardial samples (n/N=21/6) from HF patients, mean reductions in APD of 18, 15, 11 and 9% were observed at frequencies of 0.5, 1, 2 and 3 Hz, respectively, while in the mid-myocardial HF samples (n/N=12/3) the corresponding shortening of APD was of 15, 13, 5 and 11%. This shortening was significant for all evaluated conditions, except for stimulation at 3Hz in the mid-myocardial samples, where a non-significant decreasing trend in APD was observed (p=0.062).

Conclusions: The presence and function of SK channels in human failing ventricles are shown in a highly representative system like ventricular tissue slices. Significant APD shortening is observed upon activation of the SK channels, which is not observed in the control group. These results contribute to improved understanding of HF and can serve as a basis for the development of new diagnostic tools and therapies.