Characterization of atrial cardiomyopathy subtypes - A cellular electrophysiological comparison and evaluation of appropriate treatment options

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Funding Acknowledgements: Type of funding sources: Foundation. Main funding source(s): DFG

Background: Atrial fibrillation occurs in the context of atrial remodeling processes which are the result of an underlying atrial cardiomyopathy (AC). Insufficient understanding of the pathophysiological mechanisms behind AC contributes significantly to the fact that current clinical strategies for the treatment of atrial fibrillation are often ineffective. A systematic investigation of these cellular remodeling processes in the context of the various cardiac diseases underlying AC is still missing.

Purpose: The aim of this study was to characterize different subtypes of AC associated with common cardiac disease entities by systematic cellular electrophysiological characterization of the atria in combination with molecular and structural investigations.

Methods: For a comprehensive analysis of the molecular changes associated with AC, we characterized several mouse models of common heart diseases, including models for dilated cardiomyopathy (DCM), HFpEF, mitral regurgitation and immune checkpoint inhibitor (ICI-) mediated myocarditis. Patch clamp experiments were performed on isolated atrial cardiomyocytes to study atrial action potentials (aAP) and different ion currents contributing to the aAP. The cellular electrophysiological parameters of the different models were correlated to clinical parameters (ecg, echocardiography of the atria) of the mouse models and with data from RNA sequencing of the mice' atria.

Results: Patch clamp measurements performed on isolated left and right atrial cardiomyocytes revealed distinct differences among the examined models. In all pathophysiological models, the aAP was significantly shorter than in the corresponding wild type mice. The different ion current components we measured various changes in potassium, sodium and calcium currents. The repolarizing TASK-1 potassium current was significantly increased in all models. The DCM model caused by an R636Q mutation in the RBM20 gene showed the most severe changes in cellular electrophysiology. Considering the detected atrial changes, we investigated the effects of SGLT1 on atrial cardiomyocytes of the different models. When elevated concentrations of dapa-, empa- and sotaglipozin were administrated on atrial cardiomyocytes, a class-I-antiarrhythmic effect with reduced aAP inducibility and changes in the aAP duration could be observed.

Conclusion: Characterization of murine models of cardiac disease with respect to classification of AC subtypes revealed various electrical remodeling processes at the level of ion currents involved in aAP formation. A potent inductor of atrial proarrhythmogenity in the AC subtypes was an aAP shortening caused by an increase in repolarizing potassium currents, mediated especially by TASK-1. The most severe electrical remodeling in atria cardiomyocytes was observed in the RBM20-mutant model (DCM). SGLT1 exhibit anti-arrhythmic effects in different murine disease models and may provide future treatment options for patients with AC.