Pannexin-1 deficiency results in increased susceptibility for atrial fibrillation and a LQTS phenotype.

Donner B.C. (1), Petric S (1), Girgenrath L (1), Lahres T (1), van Weßel C (1), Zhaoping D (2), Schmidt KG (1)
(1) Paediatric Cardiology, Duesseldorf, Germany (2) Cardiovascular Physiology, Duesseldorf, Germany

Introduction: Pannexin-1 (Panx-1), a cardiac ion channel with structural homologies to connexins, is expressed at the cell membrane and the endoplasmic reticulum. Via Panx-1 ATP and calcium ions are released. In addition, Panx-1 itself gets activated by calcium ions and constitutes the large-conductance cation channel. However, the precise cardiac function of Panx-1 is still largely unknown. We performed cardiac phenotyping of the Panx-1 deficient mouse using different in vivo electrophysiological methods and techniques from cellular and molecular biology.

Methods: Surface ECGs in sedation, telemetric ECGs in unrestrained mice and during swimming and treadmill exercise were analysed. Echocardiography and invasive electrophysiology were in vivo examinations to further elucidate the functional status of Panx-1/- mice. Histochemistry, western blots and mRNA expression analysis were used for characterization cardiac Panx-1 deficiency on the molecular and cellular level.

Results: Panx-1 is stronger expressed in atria than in ventricles (n=5, p<0.001). Panx-1 deficiency does not alter cardiac histology (i.e. fibrosis or hypertrophy). Echocardiography showed no structural or functional abnormalities in Panx-1/- mice. Panx-1/- mice have a significantly higher incidence of AV-block in telemetric ECG analysis during physical activity (p<0.05, n=10). In vivo programmed electrical stimulation revealed no abnormalities in refractory periods and conduction. However, burst stimulation induced atrial fibrillation in all Panx-1 but not in wildtype mice (n=8) with a duration of up to 9 s. Surface ECGs using Avertin or Isofluran for sedation and telemetric ECGs in awake mice showed a significant QT and rate corrected QT prolongation in Panx-1/- mice compared to Panx-1/+ mice (Telemetry: Panx-1/+ QT: 44.6 ms ± 1.8 QTc 41 ms ± 3.7, n=6, Panx-1/- QT: 50.2 ms ± 2.1, QTc 47.3 ms ± 2.7, n=6, p<0.005). QTc prolongation was most pronounced at lower heart rates (p<0.001, n=6).

Conclusion: These results are the first evidence of an increased susceptibility of Panx-1/- mice for atrial fibrillation, a higher incidence of AV-blocks during activity and a LQTS phenotype, therefore further encouraging the functional role of Panx-1 in cardiac electrophysiology. Panx-1 seems to affect automaticity and repolarization in the heart and might be an interesting target for further evaluation in patients with atrial fibrillation.