

Deficiency of the cardiac potassium channel TASK-1 results in a LQTS phenotype and alters heart rate variability

Donner B.C. (1), Petric S. (1), Clasen L. (1), van Weßel C. (1), Ding Z. (2), Schmidt K.G. (1)
Children's Hospital, Department of Pediatric Cardiology and Pneumology (1), Department of
Cardiovascular Physiology, University Duesseldorf (2)

Introduction: TASK-1 is a potassium channel predominantly expressed in heart and brain. We have previously shown that TASK-1^{-/-} mice have a prolonged QT interval in surface ECGs in sedation (ketamine). Heart rate variability (time and frequency domain) is significantly impaired in TASK-1^{-/-} mice pointing to a sympathetic preponderance. The baroreflex sensitivity in TASK-1^{-/-} mice is unknown and can be evaluated by heart rate turbulence (HRT). Although TASK-1^{-/-} mice show a significant prolongation of monophasic action potential duration in isolated perfused hearts the electrophysiological role in vivo is unknown. First, we analysed rate corrected QT intervals (QT_c) in wake mice and after different drugs. Second, we evaluated the baroreceptor reflex by analyzing HRT. Third, TASK-1^{-/-} and TASK-1^{+/+} mice were characterized by programmed electrical stimulation.

Methods: Surface ECGs using different sedating drugs (avertin, pentobarbital, isoflurane) and telemetric ECGs by implanted transmitters were recorded and analysed. The HRT parameters turbulence onset and turbulence slope were determined after paced ventricular extrasystole and after ischemia/reperfusion. Programmed atrial and ventricular electrical stimulation using a transjugular octapolar catheter were performed to determine sinus node recovery time, Wenckebach point, atrial, atrioventricular and ventricular refractory periods. Atrial and ventricular vulnerability by burst stimulation before and after pharmacological stimulation with isoprenaline were studied.

Results: ECG analysis by telemetry showed a significantly prolonged rate corrected QT interval in TASK-1^{-/-} mice (TASK-1^{+/+} 43±3ms vs. TASK-1^{-/-} 49±5ms, n=6, p<0.05). In surface ECGs QT interval was significantly prolonged in TASK-1^{-/-} mice sedated with avertin and pentobarbital, two widely used drugs in mice (e.g. avertin: QT_c in TASK-1^{-/-} 48±4ms vs. TASK-1^{+/+} 37±8ms, n=13/16, p<0.0001). Of interest, isoflurane, known for its stimulatory effects on the TASK channel family, attenuates the QT_c prolongation in TASK-1^{-/-} mice. Programmed electrical stimulation revealed normal values for electrical conduction and refractoriness. No significant arrhythmia after atrial and ventricular burst stimulation was induced in TASK-1^{-/-} mice. However, turbulence onset is significantly altered in TASK-1^{-/-} mice.

Conclusion: TASK-1^{-/-} mice exhibit a phenotype of QT prolongation. The heart rate response after ventricular extrasystole is significantly abolished indicating an altered baroreceptor reflex. TASK-1 deficiency does not alter conduction velocity, refractoriness and vulnerability after electrical stimulation.