Late sodium current as a promising drug target for treatment of atrial fibrillation?
C. Poulet1; L. Fabritz2; U. Ravens3
1Imperial College London, National Heart and Lung Institute, London, United Kingdom; 2University of Birmingham, Center for Cardiovascular Sciences, Birmingham, United Kingdom; 3Dresden University of Technology, Medical Faculty Carl Gustav Carus, Dresden, Germany

Background: Slowly inactivating Na+ channels conducting “late” Na+ currents (INa, late) contribute to ventricular arrhythmogenesis under pathological conditions. It was recently suggested that INa, late also plays a role in chronic atrial fibrillation (AF). In the present study, we investigated the presence of late Na+ currents in atrial myocytes from patients in sinus rhythm (SR) and AF, and their potential influence on action potential (AP) shape.

Methods & Results: We validated 2 voltage-clamp protocols for the detection of late Na+ currents using JKQ mice (LQT3), which were previously shown to have increased INa,late in cardiomyocytes. In both protocols, Na+ channels were activated by a rectangular test pulse to -30 mV and we found that 250 ms after Na+ channel activation, current amplitude was significantly reduced upon application of 10 μM tetrodotoxin (TTX). We measured the amplitude of TTX-sensitive currents to estimate the density of INa,late and found 0.27 ± 0.06 pA/pF in ventricular cells and 0.18 ± 0.05 pA/pF in atrial myocytes. In human, TTX significantly reduced current amplitude, 50 and 250 ms after Na+ channel activation, only in cardiomyocytes from AF patients. In those cells, INa,late amplitude amounted to 0.16 ± 0.02 pA/pF versus 0.01 ± 0.01 pA/pF in SR myocytes (p < 0.001). Similar results were obtained when 30 μM ranolazine was used to block Na+ currents. In AF cells, INa,late amplitude averaged at 0.14 ± 0.02 pA/pF versus 0.04 ± 0.03 pA/pF in SR myocytes (p < 0.05). At 37°C, we detected INa,late only 50 ms after Na+ channel activation, suggesting a faster inactivation of the current at physiological temperature. Action potentials (APs) were further recorded in intact trabeculae from SR and AF patients. We found that 30 μM ranolazine significantly reduced the plateau potential in AF preparations, in line with the block of a small depolarizing current during the first 100 ms of the AP. This was not observed in SR trabeculae.

Conclusions: Taken together, these results suggest the existence of a small INa,late in atrial myocytes from patients with AF, which might participate in altering the AP shape.