

***In Silico* Investigation of the Functional Impact of SCN10A Mutations in Human Atrial Cells**

Inas A Al Nemi*, Haibo Ni, Henggui Zhang

University of Manchester
Manchester, UK

Introduction: Late sodium current (I_{NaL}), is a residual current from the peak the sodium current (I_{NaP}) that continue to flow throughout the plateau phase of the action potential (AP), with relatively small amplitude ($\sim 0.5\%$) compared with the I_{NaP} in normal cardiomyocytes. In a recent study, three gain-of-function mutations (R1588Q, A1073, and P1092) in the *SCN10A* channel (the gene encoding the voltage-gated sodium channel, I_{NaL}) have been identified in patients with atrial fibrillation (AF). However, the causative link between the identified mutations and pro-arrhythmogenesis in human atria has not been established yet. This study aimed to investigate the functional impact of the identified *SCN10A* mutations on the electrical action potentials (APs) of human atrial cells.

Methods: Hodgkin-Huxley formulations of the I_{NaL} developed by Grandi *et al.* for human atrial cell was modified and validated based on the experimental data of *SCN10A* channel on wild type (WT), R1588Q, A1073, and P1092 variants. The obtained I_{NaL} model equations were then incorporated into Colman *et al.* model for the electrical APs of human atrial cells.

Results: The gain-of-function mutations were found to (i) elevate the plateau potential to more positive value; and (ii) increase the AP duration at 90% repolarisation (APD_{90}) by $\sim 7\%$ and $\sim 9\%$ compared with WT for A1073 and P1092 mutations, respectively. The A0173/P1092 mutations exhibited an increase in the Na^+ concentration, which leads to intracellular Ca^{2+} overload via revers mode of Na^+-Ca^{2+} exchanger. The alteration of Na^+ and Ca^{2+} concentration causes electrical instability due to AP prolongation, enhanced automaticity, triggered arrhythmic activity and contractile dysfunction. Such conditions underlie the initiation and maintenance of AF. However, no noticeable change was found in AP profile of R1588Q variant.

Conclusion: The impact of *SCN10A* mutations on APD_{90} and the intracellular Ca^{2+} could have important implications to understand the mechanisms behind which mutations enhance atrial function and influence susceptibility to AF.