

***In silico* Screening of the Key Electrical Remodelling Targets in Atrial Fibrillation-induced Sinoatrial Node Dysfunction**

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The sinoatrial node (SAN) automaticity is responsible for initiating the heart rhythm. As the elderly population continues to expand, sinus node dysfunction (SND) is becoming an increasingly common medical condition in patients with atrial fibrillation (AF). AF itself may alter the function of normal SAN or promote pre-existing SND. AF is believed to shut down the normal function of SAN by long-term overdrive suppression of its activity. Although AF-induced remodelling may impair SAN function, ionic mechanisms underlying SND remain unclear. Here, this study investigated mechanisms by which AF-induced electrical remodelling promotes and perpetuates SND through biophysically detailed computer modelling. The recent Fabbri et al. model of human SAN cell and our mathematical model for human atrial cell action potential were modified to incorporate various experimental data on AF-induced changes in ionic channel currents and intracellular calcium handling. In our simulations, AF-induced electrical remodelling abbreviated atrial action potential duration (APD) and lowered heart rates. APD abbreviation can be mainly attributed to reduced I_{CaL} and increased potassium currents (I_{Ks} and I_{K1}). Down-regulation of I_f prolonged cycle length and thereby influenced the function of voltage clock in human SAN cells. Altogether, our simulated results indicate that voltage clock malfunction might be one mechanism underlying AF-induced SND and our SND mathematical model can be a useful in the design of experiments and the development of drugs.