In Silico Screening of the Key Electrical Remodelling Targets in Atrial Fibrillation-Induced Sinoatrial Node Dysfunction

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Abstract

Atrial fibrillation (AF) is believed to shut down the normal function of sinoatrial node (SAN) by long-term overdrive suppression of its activity. Although AF-induced remodelling may impair SAN function, ionic mechanisms underlying sinus node dysfunction (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.

1. Introduction

Sinus node dysfunction (SND) and atrial fibrillation (AF) frequently coexist and interact to initiate and perpetuate each other[1]. However, the complex relationship between the two arrhythmias remains ill defined. Recently, experimental studies showed that electrical remodelling (changes in I_f, I_{Ks} and *RyR*) occurred in sinoatrial node (SAN) cells in the pacing-induced canine model of AF[2, 3]. However, the mechanisms underlying AF-induced SND are poorly understood in patients.

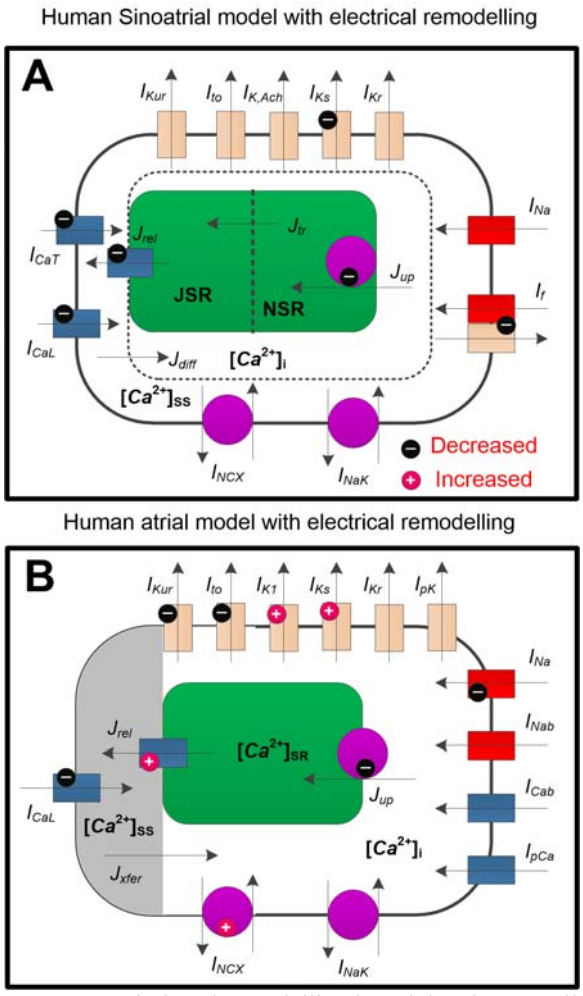

Figure 1. AF-induced remodelling in atrial and SAN cells. (A) In SAN cells, remodeled targets include I_f, I_{Ks}, I_{CaL}, I_{CaT}, J_{rel} and J_{up}. (B) In human atrial cells, an increase in J_{rel}, I_{NCX}, I_{K1} and I_{Ks}, and a reduction in I_{Na}, I_{CaL}, I_{Kur}, I_{to}, and J_{up} were observed under the AF condition.

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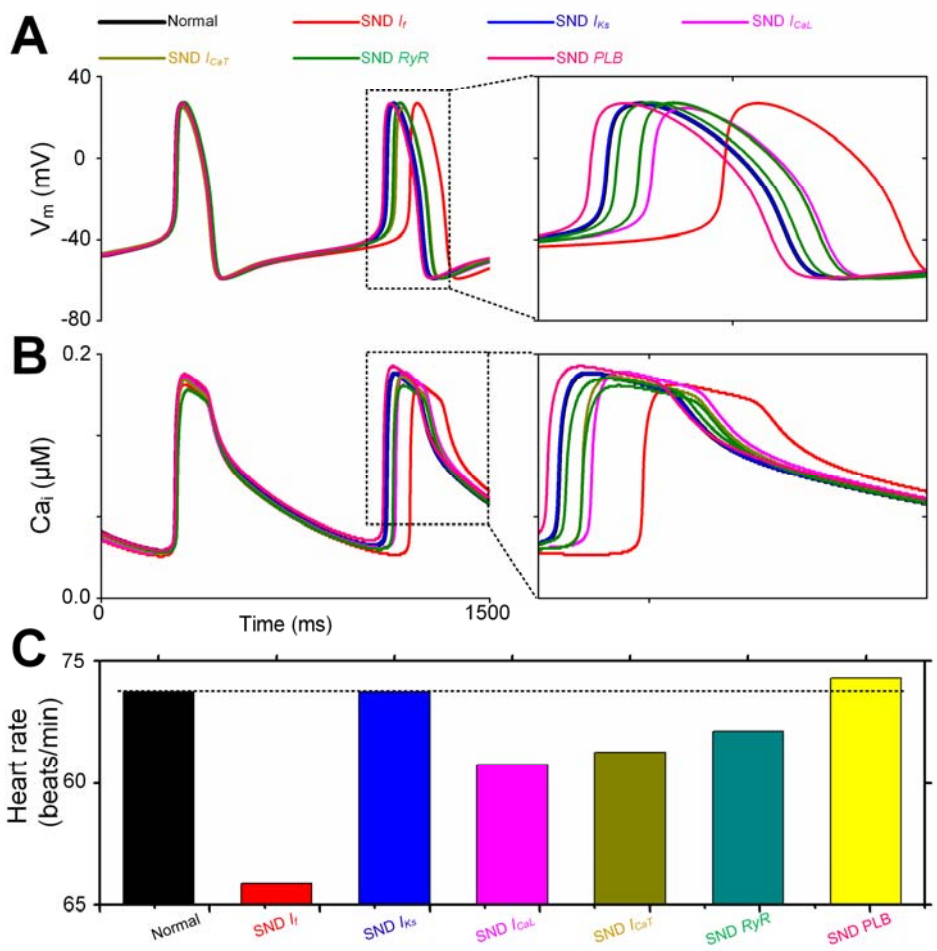

Figure 2. Effects of each remodelled target on AP (A), calcium transients (Cai, B) and heart rate (C). Remodelled targets include I_f, I_{Ks}, I_{CaL}, I_{CaT},*RyR*(J_{rel}) and *PLB*(J_{up}).

Computational models for cardiac action potentials (APs) provided valuable insights into these ionic mechanisms[4, 5]. In this study, AF-induced changes in ionic currents and calcium handling were incorporated into the recent models for human atrial and SAN myocytes. Using these models, we investigated effects AF-induced remodelling on action potentials and identified key factors, contributing to AF-induced SND at the cellular level.

2. Methods

The Fabbri et al. human SAN cell model[5] and the Bai et al. atrial cell model[4] were used as the based model for single cell simulations. In the cellular model, an ordinary differential equation was used to describe the transmembrane potential *V:*

$$\frac{dV}{dt} = -\frac{I_{ion}}{C_m} \quad (1)$$

where t is the time, C_m is the capacitance across the cell membrane and I_{ion} is the total ionic current across the membrane. For SAN cell model, I_{ion} is given by

$$I_{ion} = I_f + I_{CaL} + I_{CaT} + I_{Na} + I_{Kr} + I_{Ks} + I_{to} + I_{Kur} + I_{KACH} + I_{NCX} + I_{NaK} \quad (2)$$

For atrial cell model, I_{ion} is given by

$$I_{ion} = I_{Na} + I_{CaL} + I_{to} + I_{Kur} + I_{Kr} + I_{Ks} + I_{K1} + I_{NCX} + I_{NaK} + I_{pK} + I_{pCa} + I_{Nab} + I_{Cab} \quad (3)$$

In order to investigate effects of electrical remodelling on AP, changes in ion currents and calcium handling properties were incorporated into these cell models. In details, I_f, I_{CaL}, I_{CaT}, I_{Ks}, J_{rel} and J_{up} were decreased to 50%, 90%, 92%, 65%, 33% and 71%, respectively, for describing the SND condition. Based on experimental data on electrical remodelling in atrial cells [6], changes in J_{rel}, I_{NCX}, I_{K1}, I_{Ks}, I_{Na}, I_{CaL}, I_{Kur}, I_{to}, and J_{up} were considered.

3. Results

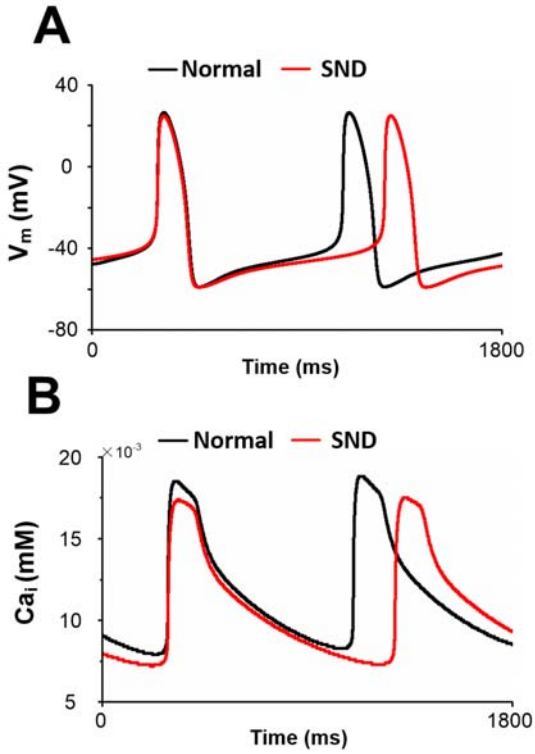

Figure 3. Comparison of action potentials (V_m, **A**) and calcium transients (Ca_i, **B**) at the superior sinoatrial node between normal and SND conditions.

To investigate how AF-induced electrical remodeling contributes to SND, effects of each remodeled ionic current/flux on SAN automaticity were studied by conducting a series of control simulations with incorporated individual ionic remodeling only. Comparison of AP (**Figure 2A**), Cai (**Figure 2B**) and heart rate (**Figure 2C**) between normal (black) and remodeled SAN cells shows that the I_f alteration mainly contributed to slow periodicity, reduced Cai amplitude and prolonged cycle length (CL) under the AF-induced SND condition. A significant reduction in the heart rate was only observed in the control model with remodeled I_f, but not under other remodeled conditions. In details, the CL increased from the control condition, 814 ms, to 911 ms, 814 ms, 848 ms, 842 ms and 816 ms, when the control model only included remodelled I_f, I_{Ks}, I_{CaL}, I_{CaT} and J_{rel}, respectively.

Single cell simulations were performed under normal and SND conditions and effects of AF-induced electrical remodeling on AP were investigated (**Figure 3**). Note that due to AF-induced electrical remodelling, the SND AP had a decrease in AP amplitude from 85.3 mV to 84.0 mV, a more gradual transition from phase 4 to phase 0 (diastolic depolarization rate, from 56.7 mV/s to 46.4 mV/s) and a small (dV/dt)max. Compared with the normal condition, the heart rate in the SND case decreased from 74 to 60 beats/min

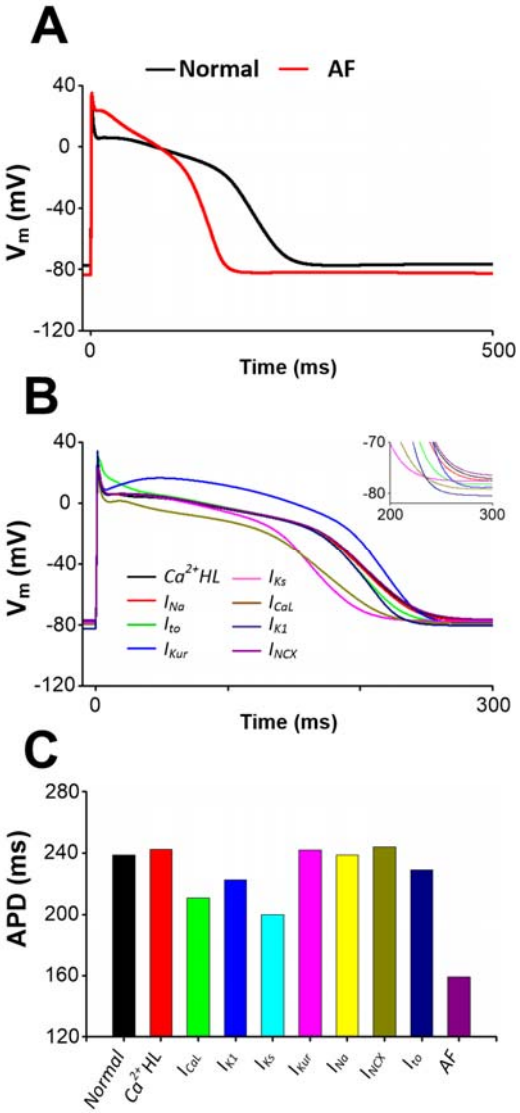

Figure 4. Effects of each remodelled target on AP and APD. (A) APs under normal and AF conditions. (B) APs under normal condition with each remodeled target. (C) APD at -70 mV during the repolarization period.

Effects of AF-induced electrical remodelling on human atrial AP were also investigated. **Figure 4A** shows APD is reduced by AF-induced electrical remodelling. However, the role of each remodeled target was different (**Figure 4B**). Changes in I_{CaL}, I_{K1} and I_{Ks} significantly decreased APD, whereas alterations in J_{rel}, I_{NCX}, I_{Na}, I_{Kur}, I_{to}, and J_{up} had no obvious effects on APD (**Figure 4C**).

4. Discussion

This study investigated effects of electrical remodelling on atrial electrical activity at the cellular level. Our main

findings are as follows: (1) AF-induced electrical remodelling caused APD shortening, contributing sustained spiral waves, and (2) the downregulation of I_f due to AF-induced remodelling led to a significantly prolonged cycle length (CL) and thereby a reduction in heart rate in SAN cells. Consequently, these findings demonstrate that electrical remodeling increases the likelihood of AF-induced SND due to APD shortening and voltage-clock malfunction, which facilitate sick sinus syndrome.

APD shortening is pro-arrhythmic. AF is characterized by a marked shortening of the atrial APD and effective refractoriness period as a consequence of alterations in the expression and function of I_{CaL} and I_K (I_{Ks} and I_{K1}). In CAF patients, the I_{CaL} decrease[7-9] and I_K increase critically contribute to the APD shortening[10]. Our results support the notion that reduced I_{CaL} and increased potassium currents (I_{Ks} and I_{K1}) mainly contribute to APD abbreviation.

The main causes of bradycardia with simulated AF are electrophysiological remodelling related to voltage and calcium clocks of the human SAN. Previous experiments on canine SAN cells have demonstrated that AF-induced remodelling of SAN ion channel expression, particularly for the "pacemaker" subunit I_f, may contribute to the clinically significant association between SND and AF[11]. Our simulated effect of I_f is concordant with these experimental findings[12].

5. Conclusion

Our simulation results indicate that voltage-clock malfunction might be the mechanism underlying AF-induced SND and our SND mathematical model for human SAN cells can be a useful in the design of experiments and the development of drugs.

Acknowledgements

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