Is insulating border necessary for human sinoatrial node spontaneous activity?

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1 Introduction

Human sinoatrial node (SAN) structure-function relationships remain poorly understood, and may be drastically different from those in smaller mammals. Recent studies based on histology for structure and optical mapping for function (e.g. see [1]) suggest that the human SAN may be electrically insulated from atrial tissue by an insulating border, except at four discrete exit pathways (SEPs) that permit atrial excitation by the SAN. Experimental data suggests that the funny current density is three fold lower in the human SAN as compared to small animals. The lower density of this important pacemaking ion channel may lead to SAN electrical activity suppression by the physiological atrial load in the absence of substantial SAN electrical insulation. In addition to experimental evidence, a recent computer modelling study provided some insights into the human SAN electrical function [2]. However, previous studies used simplified Fenton-Karma ionic model to simulate SAN activity, while a biophysically and anatomically detailed modelling has yet to be used to investigate the role of SEPs and human SAN behavior. In this study, a multi-scale biophysically detailed model of the human SAN is presented. The model is being used to investigate the role of SEPs, as well as relevant clinical conditions that promote bradycardia and brady-tachycardia.

2 Methods

As a first step, the effects of SAN-atrial coupling strength and SEP sizes and were explored using a 2D homogeneous model. Our goal was to test how different configurations of SAN-atrial coupling may affect the action potential (AP) propagation. To do so, SAN and atrial cell models, as well as a spatially extended 2D model were implemented.

2.1 Cell models

SAN cells activity was simulated with Fabbri-Severi model [3], and the Maleckar model [4] was used to simulate human atrial cell action potentials (APs). As SAN-atrial interactions are a particular focus of this study, the atrial cell model was revised. The model capacitance was increased (50 pF to 81 pF), based on experimental data. Ionic currents amplitude and intracellular volumes were rescaled by the same factor. The increased capacitance and volumes did not alter the atrial AP waveform, but augmented the current generated by the Maleckar cell model.

2.2 2D model

A 2D model of 30 mm × 30 mm consisting of atrial and SAN tissues was constructed. In accordance with previous imaging-modelling studies [2, 5] (Fig. 1E), the 2D SAN pacemaker size was taken to be a 15 mm × 3 mm ellipse for simplicity (Fig. 1A). The border of the ellipse was taken to be insulating apart from four SEPs as shown on Fig.1A. The case when an insulating border was absent was also considered. AP propagation in the tissue was simulated with conventional monodomain equation:

$$C_m \frac{\partial V}{\partial t} = I_m + D\nabla^2 V \tag{1}$$

where V is transmembrane voltage, C_m is the membrane capacitance, I_m is a sum of all model ionic currents, D is the conductivity representing cell-cell gap junction coupling. The atrial conductivity was taken equal to 1.75 $nS \cdot mm^2$ in the atrial tissue resulting in 0.2 mm/ms conduction velocity (CV), in accordance with experimental data [1]. The conductivity within the SAN tissue was varied between 0.1 $nS \cdot mm^2$ and 2 $nS \cdot mm^2$.

Conductivity at the functional SAN-atria SEPs was assumed to be equal to the conductivity within the SAN. Further, the size of the SEPs (termed as h) was altered between 1 and 3 mm (see Figure 1A).

3 Results

3.1 Estimate of SAN coupling

The SAN with insulating border was connected to the atria by four SEPs, each of which were 2 mm wide. When the SAN conductivity was taken to be 0.6 $nS \cdot mm^2$ in the SAN, steady propagation of AP from the SAN to the atrial tissue with 1106 ms cycle length (CL) (Fig.1C) was observed. Higher conductivity within the SAN resulted in longer cycle length (Fig.2). When conductivity within the SAN was increased above 1.2 $nS \cdot mm^2$, atrial hyperpolarizing load completely suppressed SAN spontaneous activity (Fig.2). When conductivity decreased below 0.4 $nS \cdot mm^2$, AP propagated from the SAN center to the border failing to depolarize the atria (Fig.1B). Thus, we observed

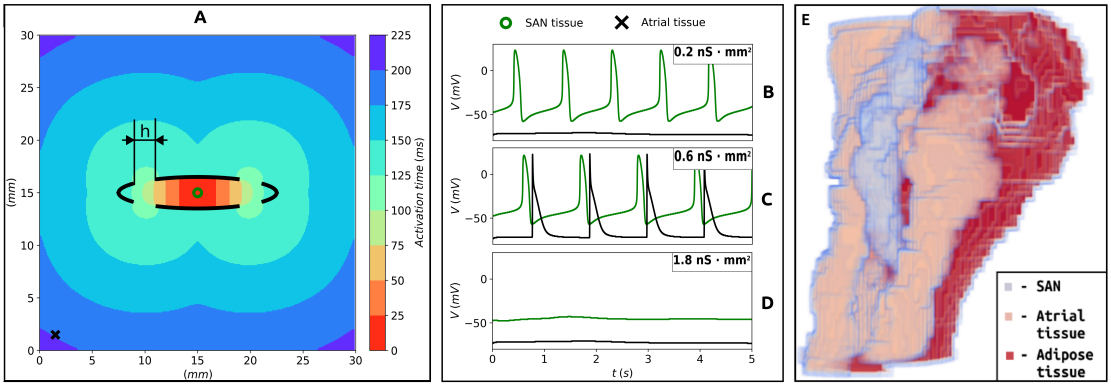

Figure 1: (A) Model geometry and activation sequence. Elliptical SAN (center) within an insulating border (solid black lines) with four SEPs. Activation sequence corresponds to the model with 2 mm wide SEPs (h = 2 mm) with 0.6 $nS \cdot mm^2$ conductivity. Action potentials recorded in spots marked by cross and circle are depicted on the right panels: (B) 0.2 $nS \cdot mm^2$ conductivity in the SAN, (C) 0.6 $nS \cdot mm^2$ conductivity in the SAN, (D) 1.8 $nS \cdot mm^2$ conductivity in the SAN. (E) Anatomically detailed SAN geometry based on [5].

a range of conductivities from 0.4 $nS \cdot mm^2$ to 1.2 $nS \cdot mm^2$ resulting in steady SAN rhythm propagating to the atria. Some parameter values close to, but outside this range resulted in more complex 2:1 activation patterns in the atria.

3.2 Effect of SEP width (h)

Simulations with wider SEPs (h = 3 mm) demonstrate that CL dependence on coupling within the SAN was more pronounced (Fig.2). Consequently, range of SAN conductivities that activated atrial tissue reduced to 0.4 $nS \cdot mm^2$ to 0.7 $nS \cdot mm^2$ (Fig.2). On the other hand, narrow SEPs (1 mm) resulted in broader "activating range" of SAN conductivities, spreading from 0.5 $nS \cdot mm^2$ to 1.9 $nS \cdot mm^2$. Importantly, in simulations devoid of an insulating border, all SAN conductivities values resulted in failure to activate the atria. When coupling in the SAN was above 0.1 $nS \cdot mm^2$, the patterns were similar to the case described above (Fig.1D), i.e. atria completely suppressed the SAN. When coupling was below 0.1 $nS \cdot mm^2$, SAN spontaneous activity failed to propagate in the atria (similar to Fig.1B).

4 Results and Discussion

These preliminary results indicate that the presence of an insulating border and SEPs may be neccessary for physiological human SAN function. In 3D, the hyperpolarizing effects of the atrial tissue on the SAN may be more pronounced. We observed most robust propagation to the atria when the SAN was connected to the atrial tissue by narrow exit pathways. Taken together, these results are in agreement with optical mapping functional studies [1] and speak in favor of the hypothesis that apart from the few exit pathways human SAN is isolated from the atria by a non-conducting insulation. This work is being extended to the biophysically and structurally detailed 3D human

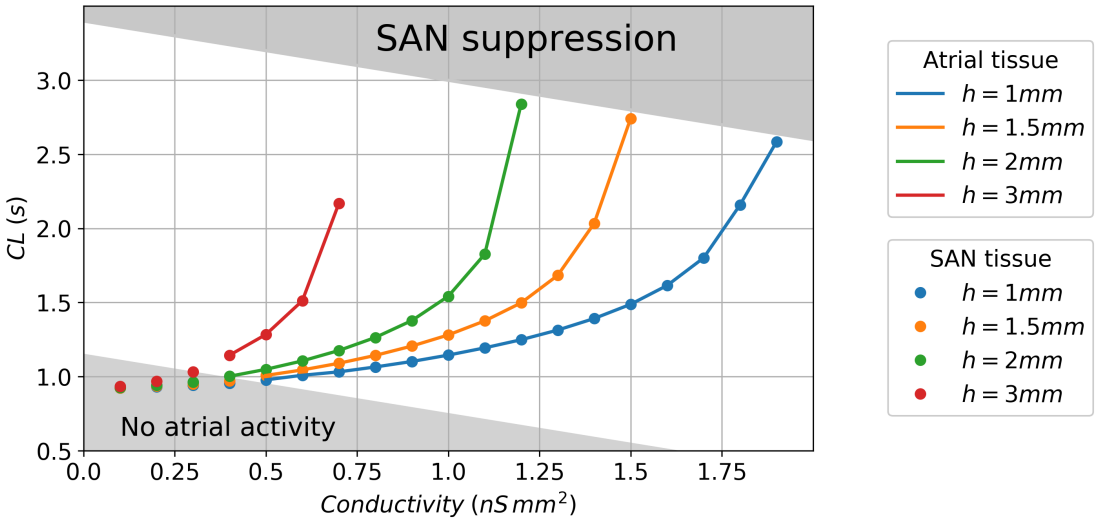

Figure 2: Dependence of action potential cycle length on conductivity in the SAN and SEPs width (h). Solid lines correspond to SAN AP propagating to atria. We observed complete SAN suppression in the upper shaded area, the SAN failed to activate the atria in the lower shaded area.

SAN model based on immunohistochemical study [5] (Fig. 1E) complemented with intranodal fibrosis that will permit further testing of the hypothesis and the role that SEPs could play in SAN dysfunction.

References

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