Activities of the sinus node pacemaking during the simulated atrial reentry

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ABSTRACT
Numerous studies implicated the relationship between the sinus node dysfunction (SND) and atrial arrhythmias, but the pacemaker activities of sinoatrial node (SAN) during the atrial reentry before the formation of structural and electrophysiological remodeling in SAN were not well investigated. In the present study, a gradient two-dimensional model including SAN and atrium was built to reflect heterogeneities of the SAN. The reentrant wave was induced by the cross field method in the atrium. The simulation demonstrated a suppressed SAN spontaneous firing by the invading reentry and a 4:1 entrance block into the SAN at a reentrant cycle length of 80 ms. When the retrograde electrical excitation from atrium captured the SAN cell, the maximum diastolic potential of its action potential was found to become more negative with increased upstroke velocity. At the same time, the amplitudes of $I_{\text{f}}$, $I_{\text{CaL}}$ and $I_{\text{Ks}}$ were enlarged. Besides, the interactions of the atrium and SAN presented a block of the sinus firing from exiting to the atrium while protecting the central SAN from the effects of the invading reentry. These findings suggested a link between SND and atrial reentry, and therefore were helpful in explaining the role of atrial arrhythmias in SND.

KEYWORDS
Sinoatrial node cell; atrium; pacemaker activities; reentry; action potential propagation; computer simulations

1. Introduction
It is known that the heart is driven by the sinoatrial node cells (SANC).[1] The connection of an atrial cell with a SANC establishes an electrical gradient which affects their behaviors.[2,3] More studies implicate the relationship between the sinus node dysfunction (SND) and atrial arrhythmias.[4,5] The long-term pacing induced atrial fibrillation (AF) was indicated to contribute to SND in canine hearts.[6] AF-induced structural and electrophysiological remodeling in SAN was suggested to be an important substrate of SND. A recent observation in clinic provided further evidence to support the specific electrophysiological changes associated with SND in patients with AF.[7] Besides, in optical mapping experiments,[8] the study in canine hearts also demonstrated the complex interactions between SAN and AF under the conditions of acetylcholine (Ach) and isoproterenol (Iso). Ach and Iso were implicated to regulate the filtering properties of the sinoatrial conduction pathways by regulating the degree of the entrance block. Meanwhile, the SAN was found to be able to beat independently from AFL/AF reentrant activity during Ach, but it was uncertain whether or not the small animal such as rabbits had similar phenomena.

Although the reported evidence provided a possible link between SND and AF/AFL through clinical observations and animal experiments, however, whether and how the reentry in a rabbit atrium had effects on SAN pacemaker behaviors before the formation of SAN remodeling was not completely investigated. Therefore, in the present study, by using the computer simulation method, we attempted to answer this question from a mathematical and electrophysiological perspective.

2. Materials and methods
An intact two-dimensional (2D) rabbit SAN connected with an atrial tissue was built. The SAN was a slice with 30 × 10 cells in the superior to inferior vena cava direction. SAN in an adult rabbit was reported to be 6 mm × 2 mm,[9] therefore, the size of the developed SAN was set to be 3 mm × 1 mm which was approximately half the size of the SAN. The atrium was a square tissue with 70 × 70 atrial cells.[10] The lay out of the model can be found in Figure 1(a).
Electrical behaviors of the cardiac tissue can be described by the following excitation-diffusion equation with no-flux conditions at the borders,

$$\nabla \cdot (\sigma \mathbf{V}) = A_m (C_m \frac{\partial \mathbf{V}}{\partial t} + I_{ion}) \quad (1)$$

$$\frac{\partial \mathbf{V}}{\partial x} |_{x=x_{\min},x_{max}} = \frac{\partial \mathbf{V}}{\partial y} |_{y=y_{\min},y_{max}} = 0 \quad (2)$$

where $V$ is the membrane potential, $\sigma$ denotes the conductivity of gap junction, $C_m$, $t$, $I_{ion}$, and $A_m$ represent, respectively, the membrane capacitance, time, total ionic current and surface-to-volume ratio. $x_{\min}$, $x_{max}$, $y_{\min}$ and $y_{max}$ in boundary conditions correspond to the minimum and maximum values of the tissue along the $x$ and $y$ coordinate axes, respectively.

In terms of function and structure, SAN is inhomogeneous in which the central SANCs normally acts as the primary pacemaker, whereas the peripheral SANCs is for the conduction of the action potential from the center to the surrounding atrial muscle.[11,12] In order to simulate the heterogeneity, Zhang’s single SANC model was used in the present study.[13] At the same time, as in the other report,[14] the parameters like the capacitance, the conductance of the SANCs from center to periphery were altered exponentially.

Since discontinuity of the gap junction at the border of SAN and atrium, the following condition was exerted at $x=l_v$

$$\sigma_s \nabla V|_{(x-l_v)} = \sigma_a \nabla V|_{(x-l_v)} \quad (3)$$

where $l_v$ represents the length of SAN. $\sigma_s$ and $\sigma_a$ represent conductivities in the region of SAN and atrium, respectively.

The model was solved by the operator splitting method.[15] The reentrant wave was induced by the cross-field technique in atrium since it was much more consistent with the one used in animal experiments.[16] The stimulus strength of 30 $\mu$A/$\mu$F in amplitude and 2 ms in duration was applied in all simulations.

### 3. Results

#### 3.1. Atrium load on SAN excitation

Figure 1 displays the depolarizing and repolarizing processes of the excitation and action potential conduction. As shown in (a), a spontaneous excitation was initially generated in the central SAN, and then conducting toward the periphery. After the SAN-atrial border was driven to fire in (b), the whole square-shaped atrium at the right hand was gradually activated ((c)). As displayed in (d), during the repolarization the peripheral SANCs and its surrounding atrial muscle repolarized first followed by the central SANCs and the atrial cells far from the SAN-atrial border.

From the action potential conduction in (e), one can find different morphologies of the action potentials. The peripheral cell exhibited a short action potential duration (APD), but more negative maximum diastolic potential (MDP) and faster upstroke velocity (UV). For the central SANC, the measured MDP and UV were $-55$ mV and 3.9 mV/ms. For the peripheral SANC, the measured MDP and UV were $-80$ mV and 14.3 mV/ms. Obviously, the central SAN fired first under the control condition.

#### 3.2. Pacemaker behaviors during atrial reentry

Figure 2 shows pacemaker activities in the developed tissue after the reentry occurred in atrium. As inspected in (a), if the time that the reentrant wave front arrived at the SAN-atrial border was coincident with the diastolic period of the SAN, the atrial depolarization wave would enter into the SAN (b) and initiate an action potential conduction from peripheral to central SANCs as denoted by the solid arrow in (e). Due to the high-speed rotation, when the reentrant wave front arrived at the junction of SAN and atrium once again (c), except that the SANCs close to the boundary could be activated, most SANCs were still in the refractory period, thus only generating an electrotonic depolarization at the periphery indicated by the dashed arrow 1 in (e). Similarly, when the reentrant wave continued to rotate and gradually approached the boundary once more in (d), due to the more recovered SANCs from the preceding excitation, compared with 1, the atrial excitation wave was able to enter and conduct a long distance (dashed arrow 2 in (e)), but with decremented amplitude and final failure. After the occurrence of another failing response indicated by 3 in (e), a repeated cycle was observed.

In order to characterize the underlying behaviors of the SAN during the atrial reentry, action potentials of the central SANC and several major currents participating in rhythmic firings are examined and displayed in Figure 3. The dashed and solid lines correspond to the control condition and the situation of the atrial reentry, respectively. As noticed in (a), when the central SANC was captured by the retrograde activation from an entering atrial depolarization wave, its MDP was reset from $-55$ mV (dashed arrow) to a more negative potential of $-59$ mV (solid arrow). At the same time, UV was raised from 3.9 mV/ms (dashed line) to 4.4 mV/ms (solid line). Compared with the control condition (dashed line), APD in the captured SANC
(solid line) declined 1.1% and 12.1% at the membrane potential of 0 mV and −40 mV, respectively.

In Figure 3(b,c,d), the hyperpolarization-activated funny current $I_f$, L-type Ca$^{2+}$ current $I_{CaL}$ and slowly activating K$^+$ current $I_{Ks}$ are exhibited. Of note, $I_f$ began to activate slowly late in the final repolarization phase and therefore was a small inward current. Due to a positive movement to its reversal potential ($−30$ mV), during the rapid upstroke it became a very small outward current. Compared with the situation of spontaneous firing (dashed line), during the atrial reentry, the amplitude of $I_f$ was enlarged by 27.8% for the captured SANC (solid line). Moreover, as an important current contributing to the fast depolarization and production of the action potential, $I_{CaL}$ exhibited an inward current property. Its magnitude was increased by 59.1% when the cell was captured by the impulse from the atrial depolarization. Similarly, as an important outward current for the repolarization, $I_{Ks}$ was raised by 259.2% as shown in (d), but no significant change (only 5.2% increment) was found for the rapidly activating K$^+$ current $I_{Kr}$ (not shown).

Moreover, if the sinus rate was elevated to 196 beats/min by increasing $I_{CaL}$ conductance, besides the similar electrical behaviors observed in Figure 2, the spontaneous firing and wave collision were found to occur in the region of SAN. As displayed in Figure 4(a), when the reentrant wave front arrived at the SAN-atrial border, a spontaneous firing had started to
appear at the central SANCs and propagated toward the periphery, but due to the retrograde activation by an entering atrial depolarization wave in (b), the spontaneous conduction was blocked and terminated at the intersection indicated by two solid arrows in (b) and (e). After that, when another reentrant rotation arrived in (c), due to the refractoriness of SAN, the poorly developed action potentials (dashed arrow in (e)) were generated at the periphery. Since more SANCs recovered from the previous excitation, when the next rotation arrived in (d), the retrograde activation entered into the SAN, but failing to conduct after proceeding a long distance (dashed arrow). Then followed by another poor response (dashed arrow), a similar cycle repeated.

4. Discussions

Heterogeneous setting plays an important role for the SAN in driving the atrium.[17] In this study, a 2D model of the intact SAN and atrium that incorporated details of electrophysiological heterogeneities from central to peripheral SAN was developed. The results in Figure 1 demonstrated consistency of our developed tissue with the observations in reported experiments.[18]

Using the model, electrical activities in SAN in the setting of atrial reentry were investigated. The main findings are the following. (1) The atrial depolarization wave could enter into and suppress the automaticity of SAN. (2) when a SANC was captured by an entering atrial depolarization wave, the MDP and currents of \( I_f \), \( I_{CaL} \) and \( I_{Ks} \) were characterized with more negative

Figure 3. Action potentials and membrane currents of the central SANC under the control condition (dashed line) and during the presence of atrial reentry (solid line). (a): action potentials. Dashed and solid arrows denote the sites of maximum diastolic potentials. (b): Hyperpolarization-activated funny current \( I_f \). (c): L-type Ca\(^{2+}\) current \( I_{CaL} \). (d): Slowly activating K\(^+\) current \( I_{Ks} \).

Figure 4. Pacemaker activities in SAN during the atrial reentry when the sinus rate was elevated. (a), (b), (c) and (d) give 4 electrical behaviors when the reentrant wave rotates in atrium. (e) displays the action potential conduction along the recording line.
potential and enlarged current magnitudes, respectively. (3) Even if the central SAN got a chance to fire and conduct the wave toward the periphery, it was unlikely to drive the atrium because of the high activating rate produced by the reentrant wave close to the SAN-atrial border.

The above findings suggested a significant role of atrium in determining the SAN electrical activities. Under the control condition, because of smaller resting potential of the atrial cell, the peripheral SANCs imposed a hyperpolarizing influence. A delayed diastolic depolarization was thus caused, resulting in a first fire in the central SANCs as demonstrated in Figure 1.

In experiments,[8] SAN was found to stand out as an oval region of lowest frequency surrounded by the higher frequency atrial region, indicating an increased SAN entrance block with increment of the pacing rate in atrium. In our present study, by inducing a sustained atrial reentry, the reentrant impulse was demonstrated to be able to enter into and suppress the SAN. A 4:1 entrance block similar to the Wenckebach phenomenon was directly observed for a reentrant cycle length of 80 ms in the atrium (Figure 2). Furthermore, when the central SANC was activated by the retrograde excitation from atrial depolarization wave, the more negative MDP and enlarged ionic currents of $I_h$, $I_{Cal}$, and $I_{Kr}$ were observed in Figure 3. The hyperpolarizing effect of the atrium and the discharge of SANC by the impulse of atrial reentry might contribute to these underlying changes. Because of the high input resistance of pacemaker, very small currents in phase 4 were reported to have relatively large effects on membrane potential.[19] Therefore, the more activated $I_h$ in phase 4 together with the injected inward hyperpolarizing current from atrial depolarization might make MDP more negative. For an SANC, the upstroke of an action potential is strongly influenced by $I_{Cal}$, so the $I_{Cal}$ increment during the atrial reentry would be the main contributor to the rise of upstroke velocity. It is known that the delayed rectifier potassium current is important in repolarization. Since $I_{Kr}$ exhibits stronger inward rectification than $I_{Ks}$ in the situation of atrial reentry, although $I_{Ks}$ showed much more significant change than that of $I_{Kr}$, the repolarizing process had no obvious alteration except a little difference in APD due to the activation of $I_{Ks}$, especially at the late repolarizing phase.

It was reported that SAN was not always suppressed by atrial pacing.[20] We found that if the intrinsic sinus rate was raised to allow firing of the central SANC, the generated spontaneous impulse would conduct from the center of the node toward the periphery, but was unlikely to activate the atrium because the SAN-atrial border already was activated at its highest possible rate by atrial reentrant wavelets (Figure 4). Thus, the influence of the atrium on SAN blocked the sinus firing from exiting to the atrium, at the same time, their interactions protected the central SAN from the effects of the invading reentry. It was not until atrial reentry terminated that concealed sinus automaticity manifested itself.

Therefore, the present study demonstrated the load effects of atrium on SAN and a link between SND and atrial reentry before the reported structural and electrophysiological remodeling in SAN was formed. Our findings will help to explain the role of atrium in SND and how the action potential and ionic currents of SANC were impacted by the retrograde impulse from an entering atrial depolarization.

Although the inhomogeneity from central to peripheral SANCs was considered in the study, the other factors like the irregular SAN-atrial border and the electromechanical couplings were not included. Additionally, our 2D tissue model was only a portion of the whole atrium, 3D tissue might more readily permit the coexistence of more than one spiral waves. This might change the electrical pattern around the SAN and the way of the effects on spontaneous firing. Therefore, 3D geometry might ultimately be required to investigate the electrical activities of the sinus node pacemaking during the atrial reentry.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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References

[1] Chen PS, Joung B, Shinohara T. The initiation of the heart beat. Circ J. 2009;74:221–225.
[2] Ronald WJ, Rajiv K, David AG, et al. Electrical interactions between a rabbit atrial cell and a nodal cell model. Am J Physiol Heart Circ Physiol. 1998;274:2152–2162.
[3] Mandel WJ, Jordan JL, Karagueuzian HS. Disorders of sinus function. Curr Treat Options Cardiovasc Med. 1999;1:179–186.
[4] Schuessler RB. Abnormal sinus node function in clinical arrhythmias. J Cardiovasc Electrophysiol. 2003;14: 215–217.

[5] Zhao J, Liu T, Li GP. Relationship between two arrhythmias: sinus node dysfunction and atrial fibrillation. Arch Med Res. 2014;45:351–355.

[6] Joung B, Lin SF, Chen ZH, Antoun PS. Mechanisms of sinoatrial node dysfunction in a canine model of pacing-induced atrial fibrillation. Heart Rhythm. 2010;7: 88–95.

[7] Chang HY, Lin YJ, Lo LW. Sinus node dysfunction in atrial fibrillation patients: the evidence of regional atrial substrate remodelling. Europace. 2013;15:205–211.

[8] Fedorov VV, Chang R, Glukhov AV. Complex interactions between the sinoatrial node and atrium during reentrant arrhythmias in the canine heart. Circulation. 2010;122:782–789.

[9] Kodama I, Boyett MR, Suzuki R, et al. Regional differences in the response of the isolated sino-atrial node of the rabbit to vagal stimulation. J Physiol. 1996;495: 785–781.

[10] Hilgemann DW, Noble D. Excitation-contraction coupling and extracellular calcium transients in rabbit atrium: reconstruction of basic cellular mechanisms. Proc R Soc Lond. 1987;230:163–205.

[11] Dobrzynski H, Li J, Tellez J, et al. Computer three-dimensional reconstruction of the sinoatrial node. Circulation. 2005;111:846–854.

[12] Li X, Zhang JQ, Shuai JW. Isoprenaline: a potential contributor in sick sinus syndrome-insights from a mathematical model of the rabbit sinoatrial node. Scientific World J. 2014;2014:540496. http://dx.doi.org/10.1155/2014/540496.

[13] Zhang H, Holden AV, Kodama I. Mathematical models of action potentials in the periphery and center of the rabbit sinoatrial node. Am J Physiol Heart Circ Physiol. 2000;279:397–421.

[14] Garny A, Kohl P, Hunter PJ, et al. One-dimensional rabbit sinoatrial node models: benefits and limitations. J Cardiovasc Electrophysiol. 2003;14: S121–S132.

[15] Zhang H, Lin SF, Yang Z. Vulnerability during short-term memory induced response in canine ventricle. Biomed Mater Eng. 2014;24:893–899.

[16] Zhang H, Zhang ZX, Yang L. Relevance of ventricular electrical dispersion to arrhythmogenesis in ischemic myocardium – a simulation study. Gen Physiol Biophys. 2005;24:365–380.

[17] Glynn P, Onal B, Hund TJ. Cycle length restitution in sinoatrial node cells: a theory for understanding spontaneous action potential dynamics. PLoS One. 2014; 9:e89049.

[18] Joyner RW, Wilders R, Wagner MB. Propagation of pacemaker activity. Med Biol Eng Comput. 2007;45: 177–187.

[19] Demir SS, Clark JW, Murphey CR, et al. A mathematical model of a rabbit sinoatrial node cell. Am J Physiol Cell Physiol. 1994;266:C832–C852.

[20] Kirchhof CJ, Bonke FI, Allessie MA, et al. The influence of the atrial myocardium on impulse formation in the rabbit sinus node. Pflugers Arch. 1987;410: 198–202.