Effects of high extracellular K^+ in atrium on pacemaker activity of sinoatrial node

Hong Zhang[1*], Zhao Yang[2], Lin Yang[3] and Shu Kong[2]
[1]School of Electrical Engineering, Xi'an Jiaotong University, Xi'an, China
[2]Medical School, Xi'an Jiaotong University, Xi'an, China
[3]Cardiology Department, the First Hospital, Xi'an Jiaotong University, Xi'an, China

Abstract: Sinoatrial node (SAN) plays a significant role in rhythmic firing in hearts. Little is known about the pacemaker activity of SAN when the extracellular K^+ concentration $[K^+]_o$ is accumulated in the atrium at the tissue level. In this paper, a gradient model of the intact SAN and its surrounding atrial muscle was developed by considering details of the SAN heterogeneous electrophysiology. The operator splitting method was used to solve the computer model. A factor *k* was introduced to $[K^+]_o$ of the atrial cell to simulate the accumulation of $[K^+]_o$. The results showed that with the elevation of $[K^+]_o$ in the atrium, the maximum diastolic depolarization of the peripheral SANCs became less negative while their action potential amplitude became smaller than that of the control condition, but little effect was found on the central SANCs. The conduction block occurred in the atrium after $[K^+]_o$ was elevated to greater than 2.5 times of its control condition. The larger the $[K^+]_o$ was, the earlier the conduction block occurred. The elevation of $[K^+]_o$ in the atrium shifted the leading pacemaker site from the center to the periphery, together with a slightly increased sinus rate. Coupling conductance within the SAN had effects on the excitation propagation in the high $[K^+]_o$ setting. For a same $[K^+]_o$, the more the conductance was enhanced, the shorter the excitation propagated away from the center. In conclusion, the high $[K^+]_o$ in the atrium was shown to modulate the pacemaker activity of SAN and impair its ability to pace and drive the atrium.

Keywords: Sinoatrial node, atrium, pacemakers, potassium ionic concentration, computer simulations.

INTRODUCTION

Sinoatrial node cells (SANCs) are the primary pacemakers of the heart. They periodically initiate action potentials to set the rhythm of the heart (Chen *et al*., 2010). A report demonstrated a gradual transition of electrophysiological properties from central to peripheral SANCs. It is this complex structure that is essential for normal functioning of the node as a whole (Dobrzynski *et al*., 2005).

Since SAN is closely coupled to the surrounding atrium, the abnormal electrical activities in the atrium were found to affect behaviors of SAN. For example, atrial fibrillation was demonstrated to result in the SAN dysfunction (Joung *et al*., 2010), an ectopic pacemaker activity in the atrium might cause abnormalities of SAN impulse generation and conduction (Zhang *et al*., 2011). Normally, in terms of function and structure, the SAN tissue is inhomogeneous in which the center of the SANCs serves as the leading pacemaker site, whereas the function of the periphery of the SANCs is to conduct the action potential from the center to the surrounding atrial muscle. However, little is known about the pacemaker activity when the extracellular K^+ concentration $[K^+]_o$ is accumulated in the atrial cell. Actually, the elevation of $[K^+]_o$ occurs in many pathophysiological situations like the hyperkalemia in electrolyte disturbances and the acute myocardial ischemia. Various symptoms of the cardiac arrhythmias like the conduction block and cardiac arrest were found to be closely related with the hyperkalemia (Vanpee *et al*., 2000), but the mechanisms are not completely understood. The disruption of the blood supply of the SAN was also observed to lead to the sinus pause, sinus exit block, or alternating bradycardia and tachycardia at the single cell level (Gryshchenko *et al*., 2002), but the effect of $[K^+]_o$ elevation in the atrium on SAN at the tissue level was unclear. Therefore, understanding how these pathophysiological situations contribute to the cardiac arrhythmias in the clinical setting is very helpful for the effective treatment. This study is to attempt to answer this question by investigating the effects of the high $[K^+]_o$ in the atrial muscle on the initiation and conduction of the pacemaker action potentials from a mathematical and electrophysiological perspective.

MATERIAL AND METHODS

Mathematical model description

Based on the single SANC (Zhang *et al*., 2000) and atrial cell models (Hilgemann *et al*., 1987), an inhomogeneous fiber was developed by coupling a series of cells through gap junctions. A monodomain system in Eq.1 was used to describe electrical behaviors of the tissue in which the electrical excitation was considered to propagate along an idealized cable:

**Corresponding author:* e-mail: mhzhang@mail.xjtu.edu.cn.

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

where V is the membrane potential, σ denotes the conductivity of gap junction, C_m is the membrane capacitance, t is the time, I_{ion} represents the total ionic current and A_m is the surface-to-volume ratio.

In order to simulate heterogeneity within the SAN region, with regards to the cellular properties, the conductance, capacitance and size of the cells were changed from the central to the peripheral SANCs in the following exponential form (Garny *et al*., 2003):

$$F_{cell} = 1.07 \times 29.0 \times \frac{1.0 \times n}{cell\_number} / (30.0 \times (1.0 + 0.7745 \times \exp((29.0 \times \frac{1.0 \times n}{cell\_number} - 24.5)/1.95))) \quad (2)$$

where F_{cell} is the scaling factor of the n^{th} cell, *cell_number* stands for the total number of cells in the region of SAN.

Cardiac tissue is generally considered as an isolated electrical medium, the current leaving the surface area is forced to be zero in terms of Neumann boundary condition. Therefore, at the left-hand and right-hand ends of the whole fiber, the no-flux boundary conditions were used,

$$(\nabla V)|_{x=0} = \nabla V|_{x=ls+la} = 0 \quad (3)$$

where x is the spatial coordinate in the string of tissue. l_s and l_a represent the length of SAN and atrium, respectively.

Since the conductivity of gap junction is discontinuous at the SAN-atrial border, a conservation of flux condition given in Eq.4 was imposed at $x = l_s$,

$$\sigma_s \nabla V|_{(x-ls)\to 0^-} = \sigma_a \nabla V|_{(x-la)\to 0^+} \quad (4)$$

where σ_s and σ_a represent conductivities in the region of SAN and atrium, respectively.

Computation and parameter selections

The operator splitting technique (Zhang *et al*., 2014) was used to split Eq.1 into two parts in which the ordinary differential equations (ODEs) describing the behavior of each single cell were solved separately from the partial differential equation (PDE) describing the electrical diffusion along the fiber. Euler method was used to solve ODEs while three-point centered difference method was applied to solve PDE.

The developed fiber included 30 SANCs and 30 atrial cells. The spatial step in the numerical solution was 0.1mm for the SAN and 0.32mm for the atrium. Thus the distance of the central SAN (at 0 mm) to the junction of the SAN with the atrial muscle was 3mm. The whole distance from the center of the SAN into the atrial muscle was 12.6mm.

A radius of 7.5μm was used for all SANCs with their length increased from 50μm for the central to 80μm for the peripheral SANCs. Intercellular conductivity was elevated from 7.5nS in the central SAN to 75nS in its periphery. For an atrial cell, the radius, length and conductivity corresponded to 10μm, 80μm and 175nS, respectively. A factor k greater than 1was introduced to $[K^+]_o$ of the atrial cell to simulate the elevation of $[K^+]_o$.

RESULTS

Action potential characteristics

Fig. 1 shows action potentials of SANCs at the left-hand end (a) and the periphery adjoining to the atrium (b) as well as the atrial cell at the right-hand end (c) along the fiber. In each plot, dot, dashed and solid lines correspond to k of 1, 1.5 and 2.5. As noticed, SANCs spontaneously depolarized to threshold and fired another action potential after the previous repolarization. Compared with the periphery in Fig.1b, the central SANC in fig. 1a was characterized with the decreased maximum diastolic potential (MDP) and upstroke velocity (UV), but long action potential duration (APD). For the control condition (dot line), the MDP corresponded to -55mV and -80mV, UV corresponded to 3.9V/s and 14.3V/s for the central and peripheral SANC, respectively. By contrast, the atrial cell (fig.1c) displayed stable and more negative resting potential (-90mV) and much greater UV (20V/s).

When $[K^+]_o$ of the atrial cell was 1.5 times of its control condition, the absolute value of the resting potential (dashed line in fig. 1c) decreased 5.6%. With further enhancement of $[K^+]_o$ to 2.5 times, its absolute value (solid line) decreased 7.8%. At the same time, the action potential overshoot and duration both declined with the elevation of $[K^+]_o$.

Fig. 1b exhibits similar alterations to the atrial cell. When $[K^+]_o$ in the atrial cell was 1.5 and 2.5 times of its control condition, MDP of the peripheral cell was raised 2.0% and 2.6%, respectively, indicating the effect of atrium on the action potential of SANC. By contrast, the central SANC in fig.1a showed little alteration in MDP and amplitude of the action potential.

Alterations of electrical propagation

When $[K^+]_o$ of the atrial cell was enhanced, different excitation waves were observed in the developed tissue model. Fig.2 shows the electrical propagation along the fiber when k was set 1, 3 and 3.5. One can find that, under the control condition (fig. 2a), SANCs were able to synchronize their firing rate by electrotonic interactions among adjoining cells via gap junctions. With the presence of atrium, the leading pacemaker site located at the upper central SANC and the excitation gradually

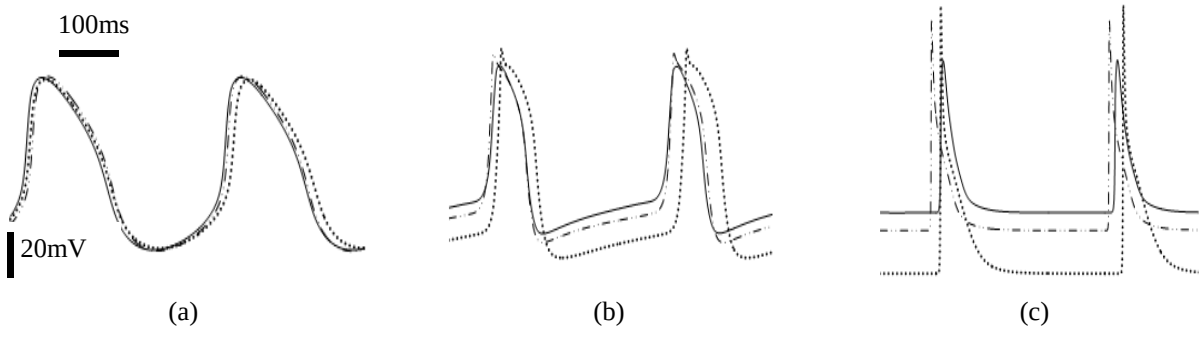


Fig. 1: Action potentials of SANCs and atrial cell for *k* of 1 (dot line), 1.5 (dashed line) and 2.5(solid line). (a): Central SANC at the left-hand end. (b): Peripheral SANC adjoining to the atrium. (c): Atrial cell at the right-hand end.

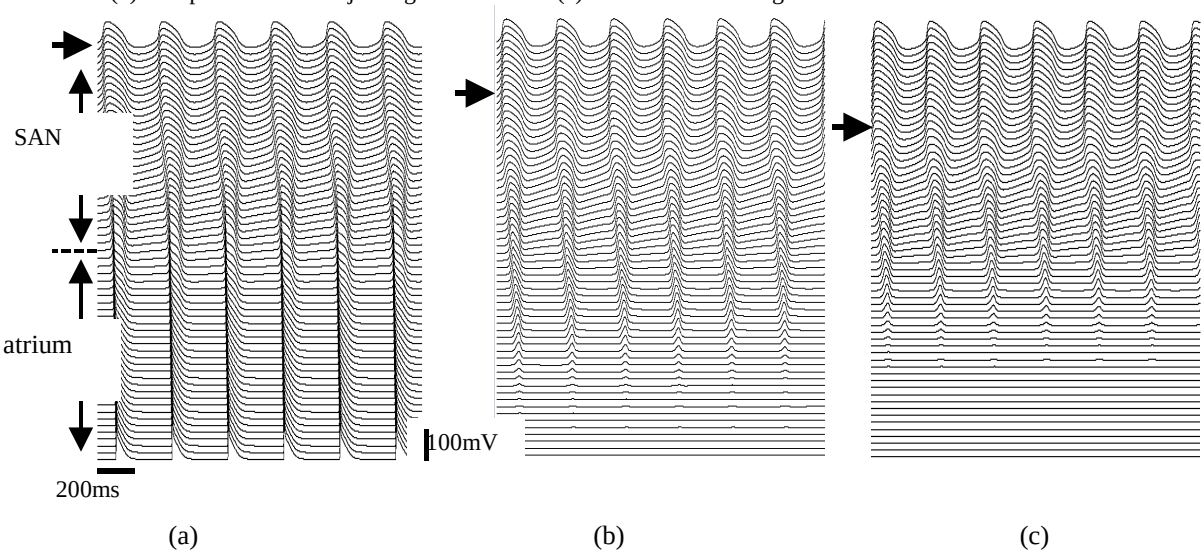


Fig. 2: Action potential propagation from the central SAN at the top to the atrial muscle at the bottom at different *k*. Horizontal arrow in each plot denotes the leading pacemaker site. (a): $k = 1$. (b): $k = 3.0$. (c): $k = 3.5$.

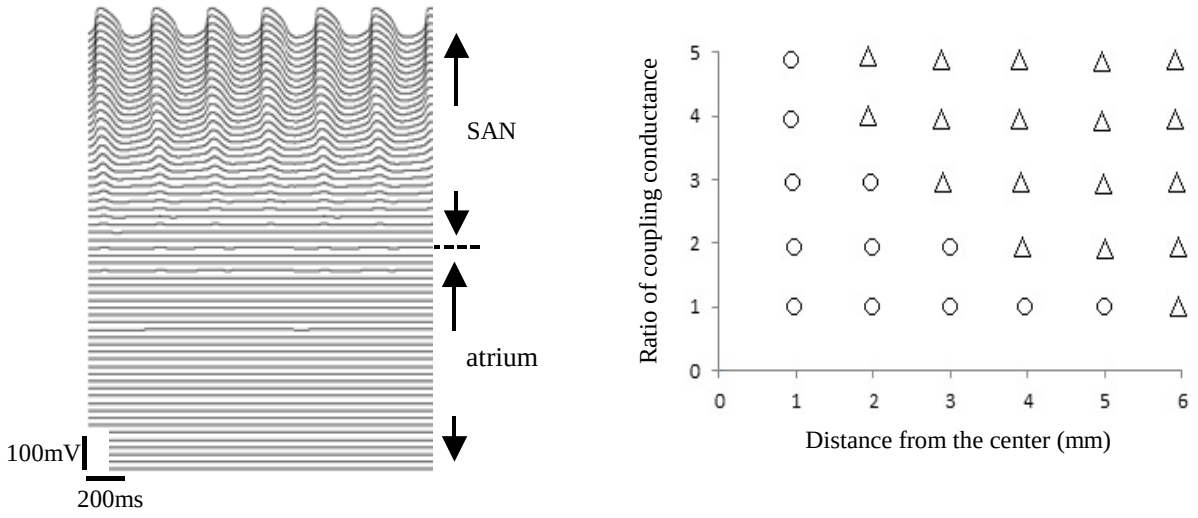
propagated to the lower periphery and drove the atrial cell to fire. The sinus rate was 174 beats/min.

When $[K^+]_o$ was elevated to greater than 2.5 times of its control condition, the propagation block started to appear. As displayed in fig.2b, the excitation was initiated in the region of SAN and propagated toward the atrium. The atrial cells close to the SANCs were able to be activated, but amplitude of the action potential became smaller and smaller with the distance away from the SAN. The cells at the remote end could not be excited and failed to produce action potentials. Moreover, as indicated by the horizontal arrows in fig.2a and fig.2b, a shift of the earliest activation site from the center to the periphery was observed. At the same time, the sinus rate was found to increase 1.5%.

Similarly, after $[K^+]_o$ was elevated to 3.5 times (fig.2c), the propagation block in the atrial side and the leading pacemaker site shift in the SAN were both observed. Nevertheless, compared with fig.2b, the number of atrial cells that could be fired had a further reduction. At the same time, the earliest activation site moved to the point indicated by the horizontal arrow which was further close to the periphery. The sinus rate increased 2.7% relative to the control condition.

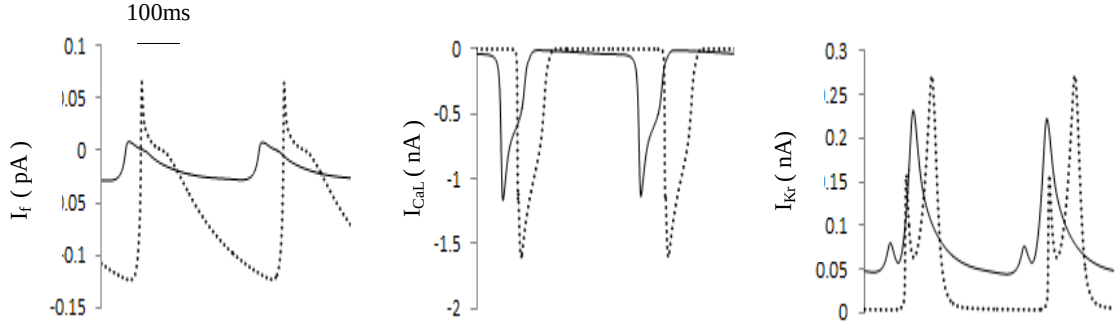
Effects of SAN gap junction

When the intercellular electrical coupling within the SAN region was enhanced, the excitation wave block was found to extend from the atrial region to SAN. Fig.3 shows the effect of gap junction conductance within the SAN on the action potential propagation when *k* was 3.5. If the amplitude of an action potential less than 30% of its normal value was considered as a failing fire, then as shown in fig.3a, when the conductance was set 4 times of its control value, the electrical wave was only able to propagate less than 2mm away from the center. The peripheral SANCs and atrium both failed to get excited. Fig.3b summarizes the conduction along the fiber when the conductance was enhanced. As inspected, if the conductance had no change (the bottom row), the



(a) (b)

Fig. 3: Effects of SAN gap junction on the conduction when *k* was 3.5. (a): Action potential propagation when the conductance within the SAN region was set 4 times of its control value. (b): Summary of the excitation propagation along the fiber with enhancement of the conductance. The *x*-axis is the distance away from the central SAN. The *y*-axis is the ratio of the enhanced conductance and its control value. The circle represents a successful fire while the triangle denotes a failing activation.



(a) (b) (c)

Fig. 4: I_f, I_{CaL} and I_{Kr} in SANC. Dot and solid lines are for k =1 and 3.5, respectively.

conduction block occurred in the atrial side about 6mm away from the center. When the conductance was doubled, the excitation was able to propagate within the SAN region, but failed to drive the atrium to fire. After further enhancement of the conductance, the peripheral SANC started to lose its spontaneous firing. The more the gap junction conductance was enhanced, the shorter the excitation could propagate from the center.

Ionic currents in SANCs

To investigate the underlying effects of the high atrial $[K^+]_o$ on SANCs, several major currents responsible for rhythmic firing of SANCs were examined. Hyperpolarization-activated funny current I_f is the inward current activated when the cell membrane hyperpolarizes, thus tending to depolarize the cell membrane and maintaining the low resting potential. L-type Ca^{2+} current I_{CaL} is a major inward current contributing to the fast depolarization and production of the action potential. Rapidly-activated K^+ current I_{Kr} is an outward current which is responsible for the repolarizing phase of an action potential. Fig. 4 shows I_f (a), I_{CaL} (b) and I_{Kr} (c) when $[K^+]_o$ in the atrium was in the control (dot line) and enhanced (solid line) situations. As inspected, in contrast with the control condition, when $[K^+]_o$ was enhanced, I_{Kr} had a residual value of 0.05nA instead of 0 at the diastolic period while amplitudes of I_f, I_{CaL} and I_{Kr} declined 81.9%, 29.8% and 37.1%, respectively. It was demonstrated that I_{CaL} and I_{Kr} blocking could result in the cessation of spontaneous firing (Zhang *et al*., 2000). So their decline indicated an inhibition effect of the high atrial $[K^+]_o$ on the SANC automaticity.

DISCUSSION

Heterogeneous setting is known to be important for the dependable functioning of SAN as the pacemaker of the heart. It allows the SAN to drive the surrounding atrial muscle without being suppressed electrotonically while promotes antegrade propagation of excitation from the SAN to the atrium. In this study, the heterogeneous setting was simulated by considering a gradual change in

the intrinsic properties of SANC from the center to the periphery. The results in fig. 1 (dot lines) and fig. 2a demonstrated that action potentials and their propagation in the developed fiber were able to reproduce observations in experiments (Joyner *et al*., 2007).

Using the developed model, the effects of the high $[K^+]_o$ in the atrium on the SAN electrical behaviors were evaluated. The main findings are the following. 1) With the elevation of $[K^+]_o$ in the atrium, MDP of the peripheral SANCs became less negative while their action potential amplitude became smaller than that of the control condition, but little effect was found on the central SANCs. 2) The conduction block occurred in the atrium after $[K^+]_o$ was elevated to greater than 2.5 times of its control condition. The larger the $[K^+]_o$ was, the earlier the conduction block occurred. 3) The elevation of $[K^+]_o$ in the atrium shifted the leading pacemaker site from the center to the periphery, together with a slightly increased sinus rate. 4) Coupling conductance within the SAN had effects on the conduction in the high $[K^+]_o$ setting. For a same $[K^+]_o$, the more the conductance was enhanced, the shorter the excitation propagated away from the center.

The above findings suggested a significant role of atrium in determining the SAN electrical activities. Under the control condition, the atrial cell had more negative resting potential than the diastolic potential of SAN cell. Therefore, the atrium exerted a hyperpolarizing effect on the peripheral SANC, resulting in a delay of the diastolic depolarization and firing of the peripheral SANC, making the central SANC a leading pacemaker site.

When $[K^+]_o$ in the atrium was elevated in some pathophysiological circumstances like the hyperkalemia and ischemia, the atrial action potential would characterize with shorter APD and less negative resting potential as well as lower excitability, therefore, more source current was required to activate an atrial cell. However, I_f, I_{CaL} and I_{Kr} currents in SANC were found to down-regulate in the high atrial $[K^+]_o$, thereby leading to the conduction block in the atrium due to the suppression of spontaneous pacemaker activity and decrement of the source current injecting into the atrium.

At the same time, as a load of SAN, atrium exerted the influence on SAN through electrotonic interactions. Because of the less negative resting potential in the setting of the high atrial $[K^+]_o$, hyperpolarizing effect of the atrium on the peripheral SANC became less significant, making the periphery more prominent in determining behaviors of the intact SAN. The intrinsic pacemaker activity of the peripheral tissue was reported faster than that of the central tissue (Li *et al*., 2014), thus resulting in a shift of leading pacemaker site from the center to the periphery, together with a slightly increased sinus rate. In a report (Kirchhof *et al*., 1987), by cutting away the atrial muscle, a shift of the earliest pacemaker site from the center to the periphery and an elevation of the pacemaker rate were observed. This observation was similar to the present study, indicating the load effect of atrium on the sinus rate and pacemaker site.

What's more, when the gap junction conductance within the SAN was enhanced, the electrotonic interactions between the center and periphery were strengthened. In this situation, the atrium would exert more influence on SAN through the peripheral SANCs, thus leading to the appearance of conduction block within the SAN region as observed in fig. 3.

CONCLUSION

The $[K^+]_o$ accumulation in the atrium can be observed in situations like the hyperkalemia and acute ischemia, but its effects on the pacemaker activities are not completely understood. In this paper based on the developed tissue model, the ability of the SAN to pace and drive the atrium was found to be compromised due to the decline of I_f, I_{CaL} and I_{Kr} currents. The enhancement of SAN gap junction would aggravate the impairment by further suppressing the SAN automaticity and leading to the conduction block. These findings are very helpful for understanding the cardiac arrhythmias as the result of the SAN abnormalities in the setting of the high atrial $[K^+]_o$.

Computer simulations are very useful methods to quantitatively study mechanisms of cardiac arrhythmias, however, due to the limitation of the tissue model developed in this study, some factors like the electromechanical couplings were not considered. Therefore, further animal experimental studies are expected to prove the present findings in this paper.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Nos. 81271661, 30870659), the Health Foundation of Shaanxi province in China (08D23), the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry (SRF for ROCS), and the Fundamental Research Funds for the Central Universities.

REEFRENCES

Chen PS, Joung B and Shinohara T (2010). The initiation of the heart beat. *Circ*., **74**(2): 221-225.

Dobrzynski H, Li J, Tellez J, Greener ID, Nikolski VP and Wright SE **(**2005). Computer three-dimensional reconstruction of the sinoatrial node. *Circ.,* **111**(7): 846-854.

Garny A, Kohl P, Hunter PJ, Boyett MR and Noble D (2003). One-dimensional rabbit sinoatrial node

models: benefits and limitations. *J. Cardiovasc Electrophysiol.*, **14**(10): S121-S132.

Gryshchenko O, Qu J and Nathan RD (2002). Ischemia alters the electrical activity of pacemaker cells isolated from the rabbit sinoatrial node. *Am. J. Physiol. Heart Circ. Physiol.*, **282**(6): H2284-H2296.

Hilgemann DW and Noble D (1987). Excitation-contraction coupling and extracellular calcium transients in rabbit atrium: Reconstruction of basic cellular mechanisms. *Proc. R. Soc. Lond.*, **230**(1259): 163-205.

Joung B, Lin SF, Chen ZH and Antoun PS (2010). Mechanisms of sinoatrial node dysfunction in a canine model of pacing-induced atrial fibrillation. *Heart Rhythm.*, **7**(1): 88-95.

Joyner RW, Wilders R and Wagner MB (2007). Propagation of pacemaker activity. *Med. Bio. Eng. Comput.*, **45**(2): 177-187.

Kirchhof CJ, Bonke FI, Allessie and Lammers WJ (1987). The influence of the atrial myocardium on impulse formation in the rabbit sinus node. *Pflugers Arch.*, **410**(1): 198-202.

Li X, Zhang JQ, Shuai JW (2014). Isoprenaline: a potential contributor in sick sinus syndrome-insights from a mathematical model of the rabbit sinoatrial node. *Scientific World J.*, **2014**: 1-11.

Vanpee D and Swine CH (2000). Elderly heart failure patients with drug-induced serious hyperkalemia. *Aging Clin. Exp. Res.*, **12**(4): 315-319.

Zhang H, Holden A.V and Kodama I (2000). Mathematical models of action potentials in the periphery and center of the rabbit sinoatrial node. *Am. J. Physiol. Heart Circ. Physiol.*, **279**(1): 397-421.

Zhang H, Lin SF and Yang Z (2014). Vulnerability during short-term memory induced response in canine ventricle. *Bio-Med. Mater. Eng.*, **24**(1): 893-899.

Zhang H, Wang J and Wu RJ (2011). Effects of atrium on the electrical activity of sino-atrial node. *Key Eng. Mater*, **467**: 742-747.