



Original Article

Simulation of ventricular rate control during atrial fibrillation using ionic channel blockers

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ABSTRACT

Background: The atrioventricular (AV) node is the only compartment that conducts an electrical impulse between the atria and the ventricles. The main role of the AV node is to facilitate efficient pumping by conducting excitation slowly between the two chambers as well as reduce the ventricular rate during atrial fibrillation (AF).

Methods: Using computer simulations, we investigated excitation conduction from the right atrium to the bundle of His during high-rate atrial excitation with or without partial blocking of the calcium or potassium ionic current.

Results: Our simulations revealed differences in rate reduction and repolarization effects between calcium and potassium current blocking and high degree of potassium current blocking required to reduce the ventricular rate during AF.

Conclusions: Our simulation results explain why potassium current blockers are not recommended for controlling ventricular rate during AF.

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1. Introduction

Electrical excitation in the heart is initiated in the sinoatrial node and is conducted sequentially to the atria, atrioventricular (AV) node, bundle of His, left and right bundle branches, Purkinje fiber network, and ventricles [1] (Fig. 1A). In the AV node, the electrical conduction speed is approximately 5 cm/s, which is 10 times slower than in the atrium [2]. The slow conduction in the AV node facilitates efficient pumping of blood by creating a delay between atrial and ventricular systole.

Atrial fibrillation (AF) is the most common sustained clinical arrhythmia. One strategy of treating AF is rate control to reduce ventricular rate, which allows AF to persist. Many reports, such

as, those from the AFFIRM study [3], suggest that rate control appears to be at least equivalent to another strategy, i.e., rhythm control, within the spectrum of currently available pharmacological therapeutic options. In the rate control therapy, the AV node is the target that determines the ventricular rate during AF. Calcium channel blockers are usually administered to control the ventricular rate, whereas potassium channel blockers are avoided. Calcium channel blockers are expected to reduce AV node excitability due to low expression of *SCN5A*, the gene encoding the sodium current protein Nav1.5 in the compact AV node [4]. On the other hand, potassium channel blockers are expected to prolong the duration of action potential and refractory periods. Class III antiarrhythmic drugs such as ibutilide increase action potential duration (APD) largely by blocking rapidly activating delayed rectifier potassium current [5] without affecting the PR interval in electrocardiogram (ECG). Therefore, longer refractory

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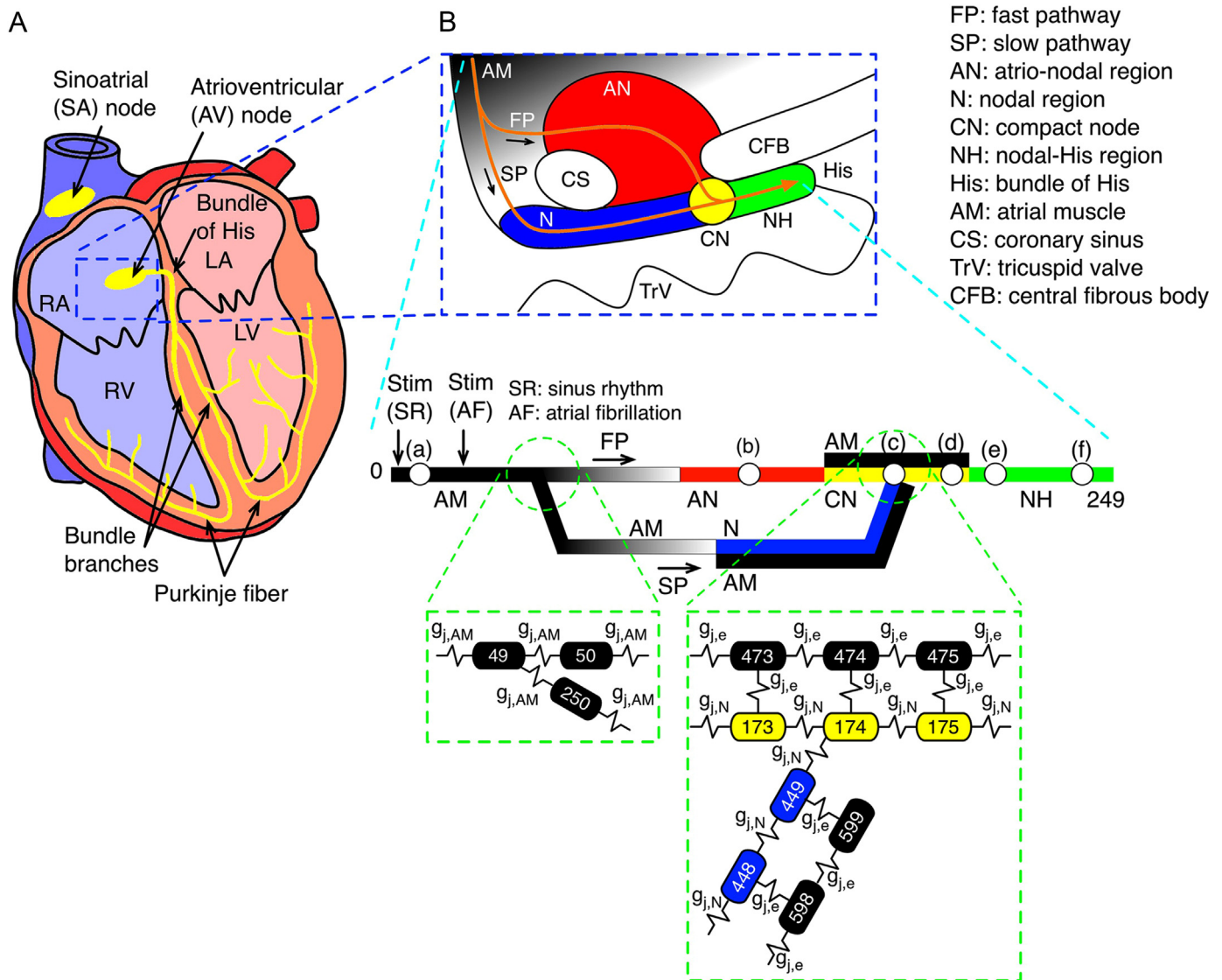


Fig. 1. Relationship between the cardiac conduction system and two types of 1D models. A: The cardiac conduction system. RA: right atrium, LA: left atrium, RV: right ventricle, LV: left ventricle. B: Relationship between the atrioventricular (AV) node (a detailed view is shown) and its one-dimensional model. For details of the models, such as the numbers of units, gap junction conductance, and characteristics of each unit, see the Methods section.

periods are expected to result in less conduction in the AV node when excitation rates in the atrium are high, such as during AF. However, the ionic basis of the rate control is not clearly understood. Understanding how these drugs control the ventricular response during AF may advance clinical treatment strategies. However, it is difficult to observe directly the effects of drugs on electrical excitation conduction in the AV node because non-invasive measurement of the AV node signal is impossible. Computer simulation is one of the methods to solve this problem. Although many electrophysiologically detailed mathematical models are available to simulate action potentials of cardiomyocytes, there are few such models for myocytes in the AV node. Recently, we constructed action potential models for the rabbit AV node, including atrio-nodal (AN), nodal (N), and nodal-His (NH) cells [6]. Using these models and an action potential model of the rabbit atrial myocyte [7], we have constructed a one-dimensional (1D) multicellular model of the region from the right atrium to the bundle of His through the AV node (Fig. 1B). Recently, Boyle et al. conducted a simulation study using Purkinje fibers, whole ventricles, and our AV node 1D model [8].

We also conducted simulations to investigate the mechanisms of excitation conduction in the AV node and ventricular rate control during AF [9]. However, we have not previously analyzed in detail the mechanisms that may explain why calcium channel blockers are suitable for ventricular rate control during AF but potassium channel blockers are not. The study aimed (1) to analyze, in detail, excitation conduction along the AV node to explain the mechanisms of ventricular rate control during AF and (2) to clarify the reason why potassium channel blockers are not efficient in controlling ventricular rate during AF.

2. Material and methods

2.1. Action potential models for rabbit cardiomyocytes

Our 1D AV conduction simulation included four types of action potential models: the atrial cell (AM cell) model developed by Lindblad et al. [7] and the three AV node cell models (the

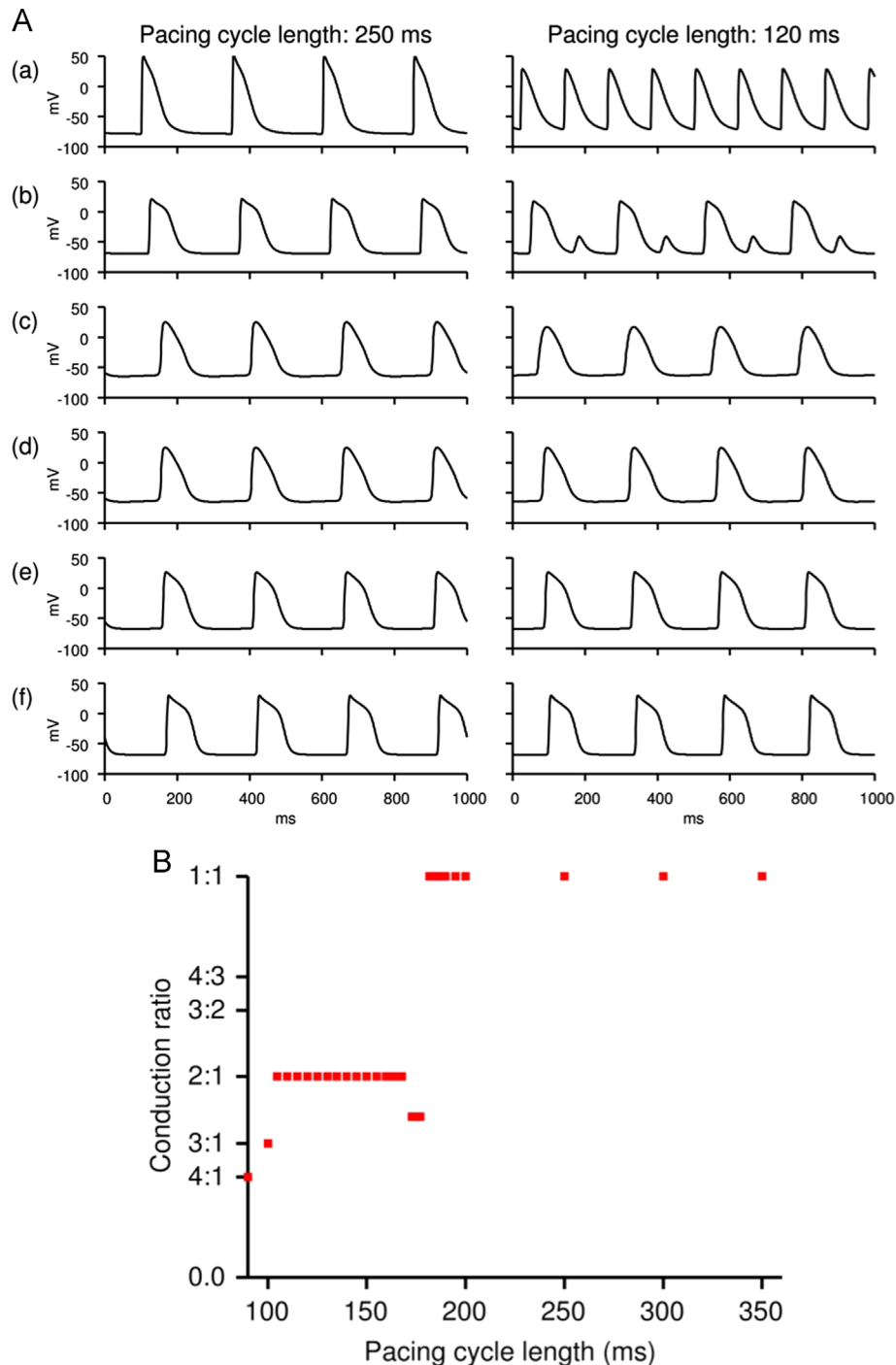


Fig. 2. Reduction of atrioventricular (AV) excitation conduction with shortening of the pacing cycle in a one-dimensional model. A: Action potential responses from 6 points of the one-dimensional model during constant pacing from the atrial end using representative slow (250 ms) and fast (120 ms) pacing cycles. Panels (a) through (f) represent the atrium, atrio-nodal region, compact node, distal His region, proximal His region, and His region, respectively. Excitation is conducted fully to the AV node at a moderate pacing cycle length, while a 2:1 conduction is observed with fast pacing. B: The relationship between the atrial pacing cycle length and the AV conduction ratio. The conduction ratio decreased when the atrial pacing cycle length was reduced.

compact AV node (N), the atrio-nodal (AN), and the nodal-His (NH) cell models) developed by us [6]. These models utilize Hodgkin-Huxley type differential equations [10]. The simulation program was written using C++, with a message-passing interface (MPI) employed for parallel computation of action potentials using multiple CPUs. To solve the ordinary differential equations numerically, a Runge-Kutta-Fehlberg numerical integration (RKF45) method was used [6].

2.2. Anatomical 1D model

Fig. 1B shows the 1D model composed of 600 units from the right atrium to the bundle of His via the AV node. The model has two conduction pathways (fast and slow). The strings of atrial cells corresponding to the atrial tissue around the compact AV node were connected to the strings of nodal (N) cells corresponding to the slow conduction pathway and the compact AV node. The

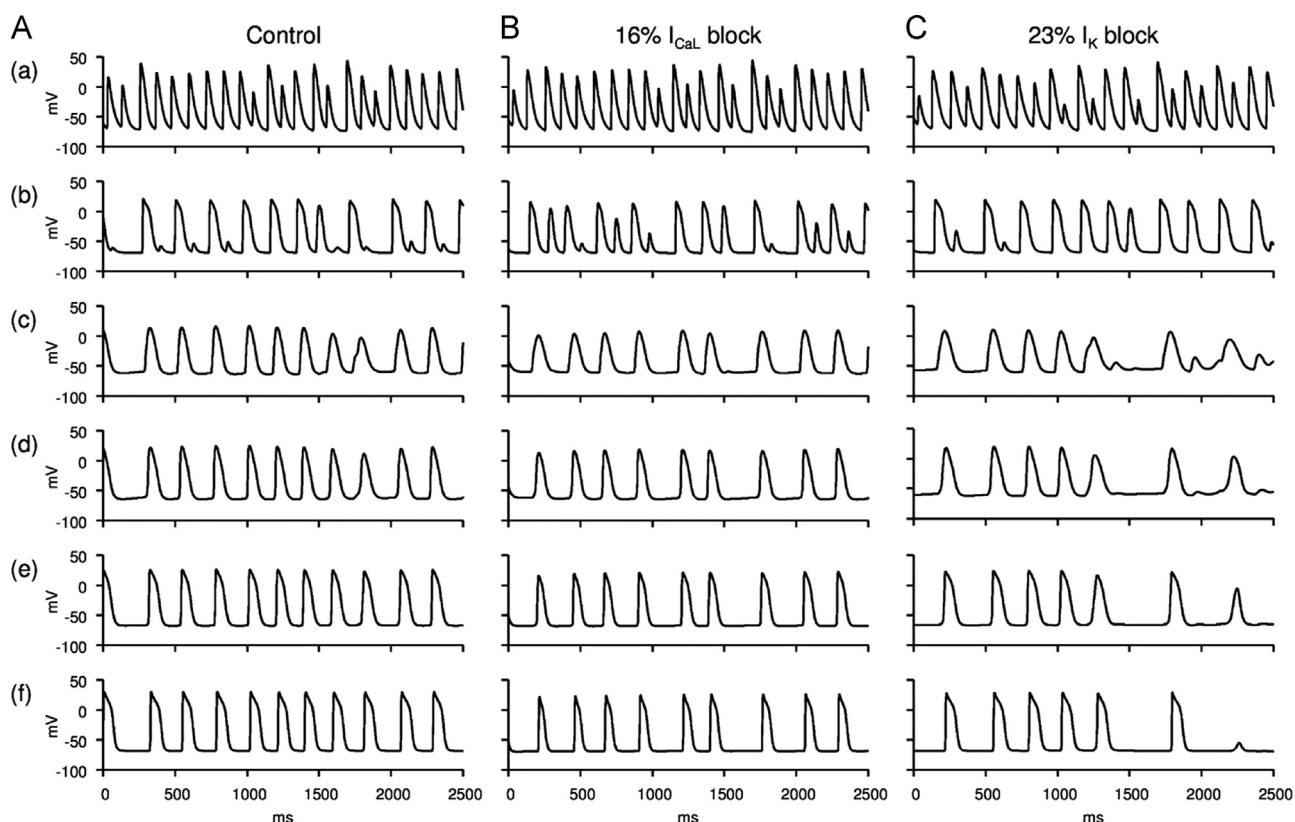


Fig. 3. Simulated action potentials recorded throughout the conduction pathway during atrial fibrillation under control conditions (A) and during ionic channel blocking (B and C). Panels (a) through (f) represent the locations indicated in Fig. 1 and listed in the legend to Fig. 2A.

conductance in the gap junction between the nodal cell strings and the attached atrial cell strings was set to 50 nS.

2.3. Simulation of excitation conduction from the right atrium to the bundle of His

To simulate excitation conduction from the right atrium to the bundle of His via the AV node, stimuli with various pacing intervals were applied at the end of the atrial string (Fig. 1B). The pacing cycle length was varied between 90 ms and 350 ms. Activation times in each cell were taken at -30 mV during the action potential upstroke [6]. To simulate excitation conduction in the AV node during AF, stimuli were applied at the middle of the atrial string. The pacing cycle length was varied randomly between 75 ms and 150 ms [11]. To simulate the effects of ionic current blocking on electrical excitation conduction at the AV node during AF, the conductance of the L-type calcium channel ($g_{Ca,L}$ current) or the rapid delayed rectifier potassium current ($g_{K,r}$) was decreased. The excitation rates in the bundle of His were represented as excitation rates per second during 20-second recordings.

3. Results

3.1. Excitation conduction in the AV node at low and high atrial rates

Fig. 2A shows representative simulation results at low and high excitation rates in the atrium. In both simulations, action potentials were obtained from (a) atrial (AM) cells, (b) atrio-nodal (AN) cells in the fast pathway, (c) compact node (CN) cells, (d) cells distal to the bundle of His, (e) cells proximal to the bundle of His, and (f) cells of the bundle of His (Fig. 1B). When the pacing cycle length was 250 ms

(Fig. 2A, left), the excitations in the atrium were fully conducted to the bundle of His. When the pacing cycle length was 120 ms, 2:1 excitation conduction was observed (Fig. 2A, right). The ratio of excitation conduction from the atrium to the bundle of His was decreased when the pacing cycle length was reduced. Fig. 2B shows the relationship between the pacing cycle length and the conduction ratio. The conduction ratio was decreased from 1:1 (pacing cycle length > 181 ms) to 4:1 (pacing cycle length 90 ms).

3.2. Ventricular rate reduction by partial ionic current blocking during AF

Fig. 3 shows simulated action potentials during AF under control (A), 16% L-type calcium channel (I_{CaL}) block (B), and 23% rapid delayed rectifier potassium channel (I_{Kr}) block (C) conditions. In all simulations, the excitation rates at the bundle of His were smaller than in the atrium. In addition, the excitation rate at the bundle of His was further decreased when the ionic current was partially blocked. Fig. 4A shows the relationship between the ratio of ionic channel blocking and the excitation rate at the bundle of His. The excitation rate at the bundle of His was gradually decreased by decreasing either I_{CaL} or I_{Kr} . When 20% of I_{CaL} or 60% of I_{Kr} was blocked, a complete conduction block at the AV node was observed. Fig. 4B shows excitation rates in six regions of the model along the conduction pathway from the atrium to the bundle of His through the fast pathway (Fig. 1B (a) through (f)). The excitation rates along the fast pathway were gradually decreased. In the control experiment, the excitation rates were decreased to 61.6%, 49.4%, 48.2%, 47.7%, and 47.7% of those in the atrium, atrio-nodal, nodal, distal, and proximal areas from the bundle of His, and the bundle of His, respectively. Fig. 5A shows action potentials in these regions when a complete AV block was simulated.

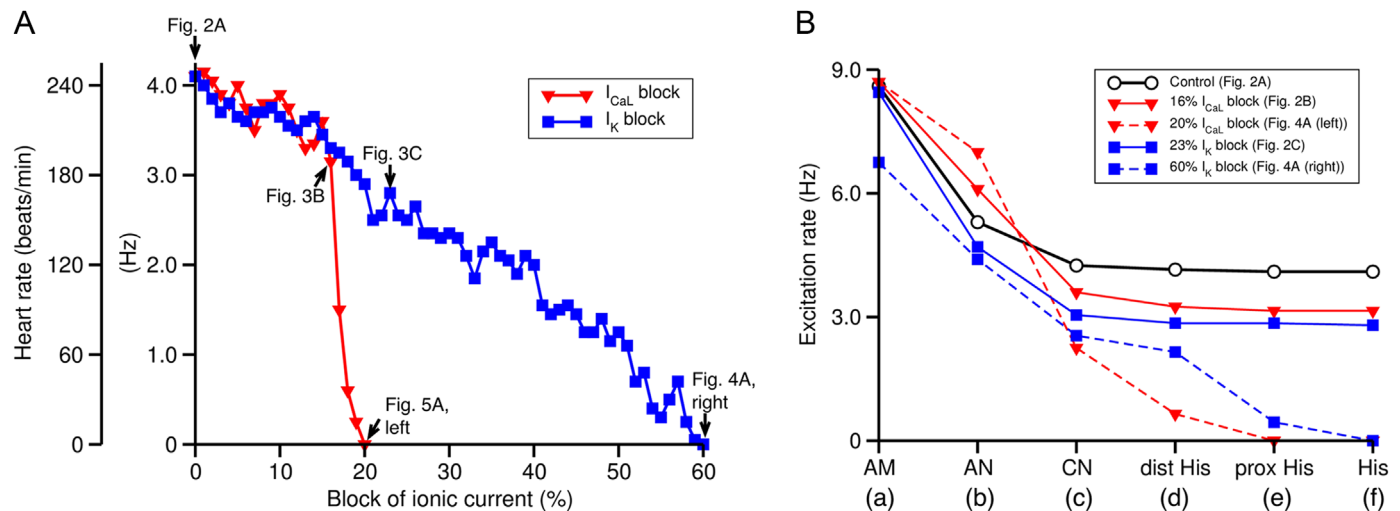


Fig. 4. Relationships between ionic current blocking and the heart rate at the bundle of His (A) and reduction of the excitation rate at 5 distal portions of the conduction pathway (B).

3.3. Effects of partial ionic current blocking on excitation conduction at the AV node in sinus rhythm

Fig. 5B shows simulated action potentials during a 20% I_{CaL} block (left) and a 60% I_{K} block (right). In the 60% I_{K} block setting, a complete AV conduction block was observed, whereas the excitation was conducted in the 20% I_{CaL} block setting.

4. Discussion

4.1. Usefulness of our modified 1D model

In this study, we improved the 1D model from a previous study [6] to simulate the compact AV node affected by atrial muscle electrotonically. The previous model did not allow simulating excitation conduction in the AV node at high excitation rates in the atrium [9]. In the previous model, the next excitation arrived from the atrium to the compact AV node before its complete repolarization (Fig. S1A, left). Therefore, recovery from inactivation of the L-type Ca^{2+} current, which is important for excitation conduction at the compact AV node, was incomplete (Fig. S1A, right). Accordingly, the compact AV node could not produce enough current for excitation of the nodal-His and His regions. A 3D AV node model constructed by Li et al. showed that AV node cells were surrounded by atrial cells [2]. Because these atrial cells might be important during the repolarization phase in the AV node, we modified our previous 1D model. The simulations showed that the modified model reproduced responses of the AV node at a high excitation rate in the atrium (Fig. S1B) and that the excitation rate in the bundle of His depended on that in the atrium. In particular, the ratio of excitation conduction between the right atrium and the bundle of His decreased from 1:1 to 4:1 with increasing excitation rate in the right atrium (Fig. 2B). These simulation results were qualitatively comparable to the results of a theoretical study by Shrier et al. [12] and experimental recordings conducted by Mase et al. [13]. Therefore, the modified 1D model is more realistic than the original model.

4.2. Ventricular rate reduction by ionic current blocking

The simulations using the modified 1D model showed that, although both Ca^{2+} and K^{+} current blocking reduced the

excitation rate in the bundle of His during AF (Fig. 4A), the mechanisms of ventricular rate reduction were different.

The slow excitation conduction and upstroke velocity of the action potential in the compact AV node (nodal cells) may be due to a small or absent Na^{+} current [14,15]. In these cells, the upstroke phase of the action potential is induced by the inward currents, such as the L-type Ca^{2+} current. In the transitional areas from the right atrium to the compact AV node (N cells) and from the compact AV node to the bundle of His (NH cells), the L-type Ca^{2+} current also acts at the initial repolarization phase. Therefore, blocking of the L-type Ca^{2+} current reduces the action potential duration and the refractory period in these cells (Fig. 3B). Moreover, high-rate excitations in the atrium, such as during AF, arrive at the compact AV node owing to the short action potential duration and refractory period in the AN region (Figs. 3B(b) and 4B, red symbols). It is possible that L-type Ca^{2+} channels in the compact AV node cannot recover from inactivation because of the high excitation rate (Fig. S2B(c), right). As a result, the excitability in these cells is reduced. Given this low excitability (Fig. 5A, left), the transitional area between the compact AV node and the NH region cannot be driven by the compact AV node. During normal excitation in the atrium, L-type Ca^{2+} channels in the compact AV node may be able to recover completely. This results in excitation conduction from the atrium to the bundle of His via the AV node, despite partial blocking of the L-type Ca^{2+} current (Fig. 5B, left).

Potassium currents in cardiomyocytes mainly affect the repolarization phase of the action potential. Therefore, blocking of the potassium currents may increase the action potential duration and refractory period. Strong blocking of potassium current prevents full repolarization of the action potentials (Fig. S2C(c), left). Therefore, sodium and calcium channels may not completely recover from inactivation (Fig. S2C(c), right). As a result, the excitations are not conducted to the bundle of His despite the low excitation rate in the atrium under conditions of low potassium channel conductance (Fig. 5B, right).

4.3. Why are potassium channel blockers not used for controlling ventricular rate?

Our simulations showed that potassium current blocking achieved a moderate control of ventricular rate compared with calcium current blocking (Fig. 4A). However, excitations were not conducted to the AV node during strong potassium channel blocking (Fig. 5A and B, right).

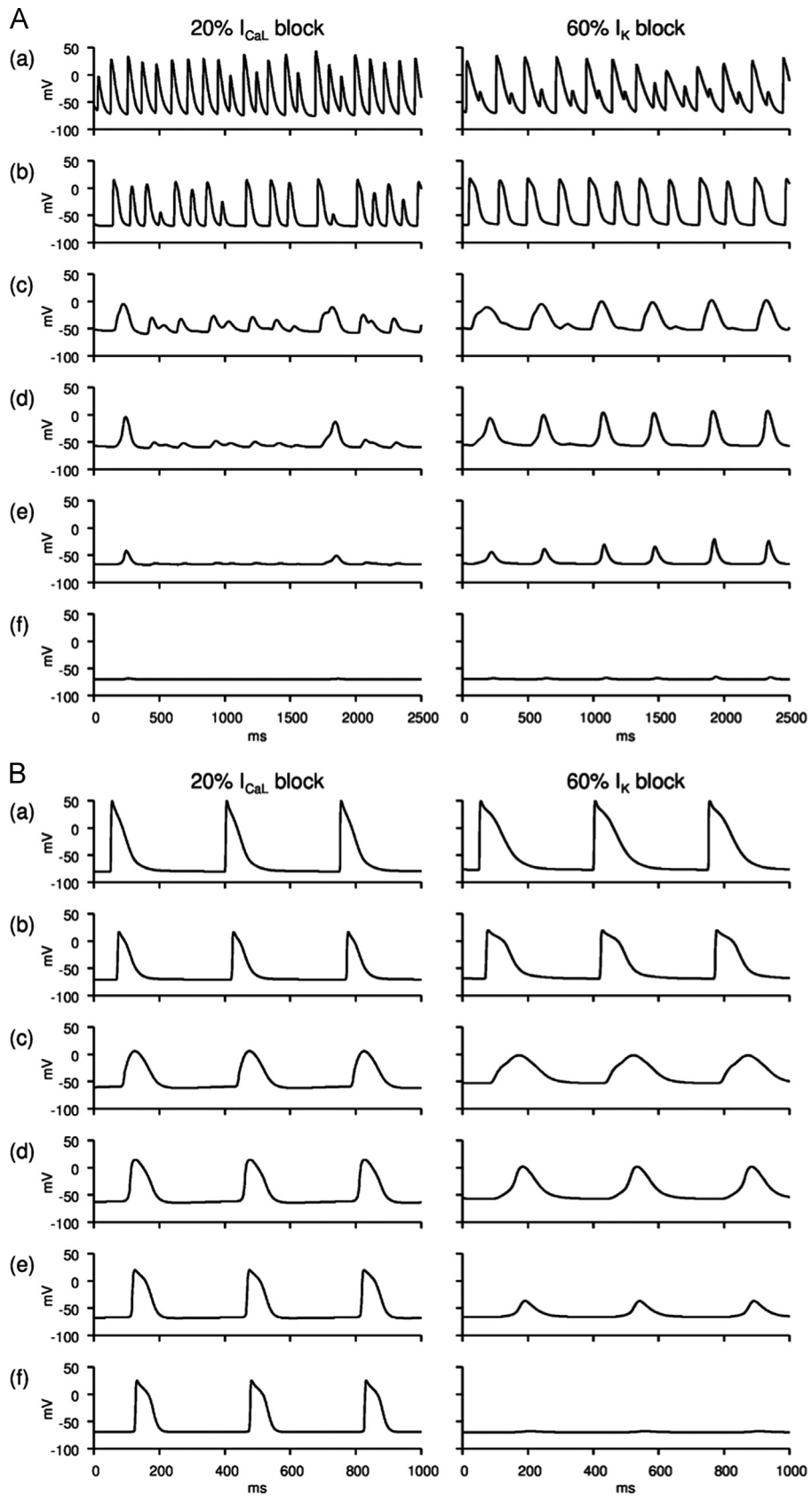


Fig. 5. The effects of strong blocking of either I_{CaL} or I_{Kf} on excitation conduction during atrial fibrillation (A) and on regular pacing with a cycle length of 350 ms (B). Panels (a) through (f) represent the locations indicated in Fig. 1 and listed in the legend to Fig. 2A.

Fig. 4A shows that both calcium and potassium current blocking can modify the ventricular rate during AF. However, it is difficult to control the ventricular rate during AF via potassium current blocking. The reasons for not using potassium channel blockers are (1) higher concentrations of potassium channel blockers required for decreasing the ventricular rate compared to calcium channel blockers (Fig. 4A) and (2) prolongation of the action potential duration and the QT interval in ECG (Fig. S3), which increases the inducibility of ventricular arrhythmias [16]. Therefore, blocking the K⁺ current might increase the arrhythmogenicity of the ventricles.

Our simulations showed that a higher concentration of K⁺ channel blockers than Ca²⁺ channel blockers might be required to control the ventricular rate during AF. However, high concentrations of K⁺ channel blockers may induce ventricular arrhythmia. For these reasons, K⁺ current blockers are not used clinically.

4.4. Limitations

Although our simulations are important for understanding the mechanisms of ventricular rate control during AF with and without ionic channel blocking, our model is a simplification of the actual anatomical structure of the AV node. There may be several pathways of conduction from the right atrium to the AV node. In addition, extracellular potential recordings by Zhang et al. suggest that multiple layers are present in the nodal-His region [17]. Our 1D model cannot investigate such complex anatomical structures. Therefore, a more realistic model, such as the 3D anatomical model developed by Li et al. [2], will be needed to simulate excitation conduction.

In this study, the employed four action potential models used atrial cells and three types of AV node cells of the rabbit. Therefore, the results cannot be compared directly with clinical data from human patients, such as the AH interval obtained via electrophysiological recordings. We have constructed action potential models for human cardiomyocytes in different regions, including the cardiac conduction system, using messenger RNA (mRNA) data [4,18]. We plan to simulate action potential conduction in the human cardiac conduction system in future studies.

Finally, beta-blockers are commonly used for ventricular rate control during AF. Therefore, it is also important to simulate the effects of beta-blockers on excitation conduction in the AV node. To our knowledge, there is not enough experimental data to simulate the effect of beta-blockers on ionic currents and excitation conduction in the AV node during AF in the rabbit and human heart. Some simulation studies showed that beta-adrenergic stimulation affects heart rate [19] and QT interval [20]. If the effect of beta-blockers is opposite to that of beta-adrenergic stimulation, it will be possible to construct action potential models to simulate the effect of beta-blockers on ionic currents and excitation conduction in the AV node in the near future.

5. Conclusions

Our computer simulations revealed the following: (1) Ca²⁺ and K⁺ current blockers could control the ventricular rate during AF, (2) a complete AV block during AF was induced by strong Ca²⁺ or K⁺ channel blocking, (3) a stronger K⁺ current blocking is required to reduce ventricular rate during AF compared with Ca²⁺ current blocking, and (4) Ca²⁺ current blockers did not prevent AV node conduction at a moderate excitation rate in the atrium, such as during sinus rhythm. These results suggest that the mechanisms of ventricular rate control may differ between Ca²⁺ current blockers and K⁺ current blockers. In addition, our simulation

results explained why K⁺ current blockers are not used clinically to control ventricular rate during AF.

Conflict of interest

All authors declare no conflict of interest related to this study.

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Appendix A. Supporting material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.joa.2016.12.002>.

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