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Simulation study of complex action potential conduction in atrioventricular node*

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Abstract— **The atrioventricular (AV) node, which is located between the atria and ventricles of the heart, acts as important roles in cardiac excitation conduction between the two chambers. Although there are multiple conduction pathways in the AV node, the structure of the AV node has not been clarified. In this study, we constructed a one-dimensional model of the AV node and simulated excitation conduction between the right atrium and the bundle of His via the AV node. We also investigated several characteristics of the AV node: (1) responses of the AV node to high-rate excitation in the right atrium, (2) the AV nodal reentrant beat induced by premature stimulus, and (3) ventricular rate control during atrial fibrillation with various methods. Our simulation results suggest that multiple conduction pathways act as important roles in controlling the ventricular rate. The one-dimensional model constructed in this study may be useful to analyze complex conduction patterns in the AV node.**

I. INTRODUCTION

The atrioventricular (AV) node of the mammalian heart is located between the atria and ventricles and is the only site where the action potential can pass between the two sets of chambers (Fig. 1, left). Slow conduction of the action potential through the AV node facilitates efficient pumping of blood by creating a delay between atrial and ventricular systole. The AV node is frequently the site of reentrant rhythms. Fast and slow pathways into the AV node are believed to be the substrate for AV nodal reentry. Therefore, the electrophysiological behavior of the AV node is important. The major roles of the AV node are to facilitate slow conduction from the atria to the ventricles to allow for ventricular filling, to slow the ventricular rate during atrial fibrillation (AF), and to provide pacemaking during failure of the sinoatrial node, which acts as a physiological pacemaker in the normal heart.

Although there are many action potential models for the sinoatrial node, atrial muscle, Purkinje fibers and ventricular muscle, there are few models of the AV node. Recently, we developed a family of biophysically detailed AV node action potential models for the atrio-nodal (AN), nodal (N) and nodal-His (NH) regions [1]. The differences in the action potential shape among these three regions likely from differences in ionic currents. We also constructed a simplified anatomical model with two conduction pathways in the AV node, and we simulated the action potential conduction from the right atrium to the bundle of His on various situations such as during AF. However, the exact anatomical substrate of a dual-pathway conduction system remains unclear. In this study, we modified the one-dimensional anatomical model and simulated action potential conduction in the AV node and the effects of blocking ionic currents.

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II. METHODS

A. One-dimensional model of the AV node

Recently, we developed action potential models for the AV node [1]. Using these models with an action potential model of the atrial muscle (AM) cell [2], we constructed a one-dimensional (1D) multicellular model from the right atrium to the bundle of His through the AV node of the rabbit (Fig. 1, right). The multicellular model has fast and slow conduction pathways in the AV node. The atrial cells were connected to two pathways. Finally, two pathways were connected to a common string of compact node cells. Neighboring cells were connected by a coupling conductance (g_j). In this study, we modified the structure of the model constructed in the previous study [1] to fit simulation results to experimental recordings including an effective refractory period of the rabbit AV node [3].

B. Simulation of action potential conduction in the AV node

To simulate action potential conduction in the AV node during sinus rhythm (physiological pacemaking generated from the sinoatrial node) and high-rate excitation corresponding to atrial tachycardia, stimuli were applied into the end of the atrial string.

C. Simulation of ventricular rate control during atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia. There are two approaches for treating AF: The first involves treatment with antiarrhythmic drugs to maintain sinus rhythm (rhythm control), and the second uses ventricular rate-controlling drugs that allow AF to persist (rate control). Many studies, including the AFFIRM study [4], have reported that the rate-control therapy appears to be at least equivalent or better than rhythm control using currently available pharmacological therapeutic options. Compared

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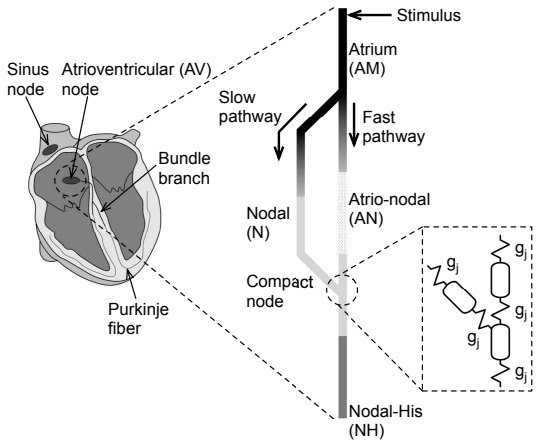

Fig. 1. Constructing a one-dimensional model of the AV node. The model was composed of 1) 50 AM cells, 2) 50 AM cells, 50 AN cells and 25 N cells composing the fast pathway, 3) 100 AM cells and 100 N cells composing the slow pathway, and 4) 25 N cells and 50 NH cells composing the transitional area between the AV node and the bundle of His.

with rhythm control therapy, rate-control treatment is simple and relatively easy. Therefore, rate control therapy is one of the most important treatments.

In rate-control therapy, the AV node may be involved in several important roles. Digitalis, Ca^{2+} channel blockers and beta-blockers are often used to control the ventricular rate in patients with AF. However, the ionic basis underlying the rate-control treatment is not clear. A better understanding of how the drugs control the ventricular response during AF may lead to the advancement of new clinical treatment strategies. In this study, the effects of digitalis, Ca^{2+} channel blockers and beta-blockers on action potential conduction from the right atrium to the bundle of His during AF were simulated. We also simulated the effects of the fast or slow pathway ablation to investigate another possibility to control the ventricular rate during AF. To simulate AF, the string of atrial cells was stimulated and the intervals of stimuli were changed randomly from 75 to 150 ms [5].

1) Digitalis: Digitalis is used to adjust the ventricular rate when AF occurs, and the application of digitalis results in increased contraction. Digitalis inhibits the Na^+/K^+ pump current and shortens the duration of the action potential. The Na^+/K^+ pump current is an important ion-regulating transporter that plays a critical role in maintaining the ionic balance across the membranes of cardiac myocytes. Elevation of intracellular Na^+ concentrations have been observed in myocytes after treatment with digitalis [6], [7]. In this study, we investigated the effects of increasing the intracellular Na^+ concentration on action potential conduction using the model.

2) Ca^{2+} *channel blocker:* Blocking Ca^{2+} current is known to block conduction through the AV node [8]. The effects of Ca^{2+} channel blockers on the ventricular response during AF was simulated to decrease the channel conductance of $I_{\mathrm{Ca,L}}$ ($g_{\mathrm{Ca,L}}$).

3) Beta-blockers: Although beta-blockers are also effective for controlling the ventricular rate during AF, it is unclear whether beta-blockers may affect ionic currents in the AV node cells. Unfortunately, only a few electrophysiological studies have recorded the ionic currents after exposure to beta-blockers. For example, Marshall et al. showed that the transient outward current (I_{to}) and the inward rectifier K^+ current ($I_{\mathrm{K},1}$) in human atrial myocytes were decreased by beta-blockers [9]. Cheng et al. showed that the L-type Ca^{2+} current ($I_{\mathrm{Ca,L}}$), transient outward current (I_{to}) and slowly activating component of the delayed rectifier K^+ current ($I_{\mathrm{K,s}}$) in rabbit ventricular myocytes were all inhibited by carvedilol [10].

To simulate the effects of beta-blockers on ionic currents of the AV node cells, we assumed that the L-type Ca^{2+} current ($I_{\mathrm{Ca,L}}$) was decreased by 5%, and the channel conductance of the rapidly activating component of the delayed rectifier potassium current ($g_{\mathrm{K,r}}$) was also decreased from 0% to 55% compared with the physiological condition to suppress AV nodal conduction.

4) Fast pathway ablation: Catheter ablation of the AV node has been proposed for control of the ventricular rate in patients with AF [11]. However, the exact mechanism of rate control is unclear. In this study, we investigated whether selective ablation of the AV node can provide sufficient reduction in the heart rate during AF.

III. Results and Discussions

A. Action potential conduction in the AV node during sinus rhythm and high-rate excitation in the atrium

During sinus rhythm (pacing cycle length: 350 ms), action potentials are conducted from the right atrium to the bundle of His via the AV node (Fig. 2 A). The fast pathway in the AV node is likely the primary conduction pathway under sinus rhythm. During high-rate excitation in the atrium, intermittent conduction occurred in the AV node (Fig. 2 B and Fig. 3).

B. AV nodal reentry induced by premature stimulus

The AV nodal reentry was induced by the premature stimulus applied to the atrium. An S1-S2 protocol was used to trigger AV nodal reentry. Fig. 4 A shows the representative result. In response to S1 stimulation (basic beat), the action potential was conducted from the atrial muscle to the bundle of His via the fast pathway of the AV node. In response to S2 stimulation (premature beat), the action potential was also conducted via the slow pathway. Slow pathway conduction exhibited slow activation with a shorter refractory period compared with the fast pathway. Excitation after premature stimulus was blocked in the fast pathway, the delayed slow pathway activation could maintain AV nodal conduction and initiate a reentrant beat.

When the S1-S2 interval was set to between 101 and 120 ms, AV nodal reentry occurred. When the S1-S2 interval was shorter than 101 ms, action potential conduction after a premature stimulus through the AV node was blocked completely (Fig. 4 B). This corresponds to the refractory period of the slow pathway.

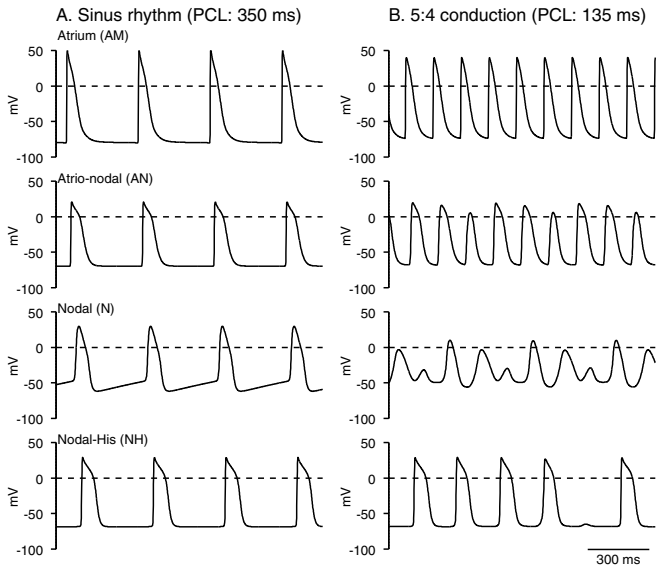

Fig. 2. Action potential conduction from the right atrium to the bundle of His. A, action potential conduction during sinus rhythm. In this simulation, a pacing cycle length of 350 ms was used. B, action potential conduction with a higher pacing rate applied to the right atrium. In this simulation, a pacing cycle length of 135 ms was used.

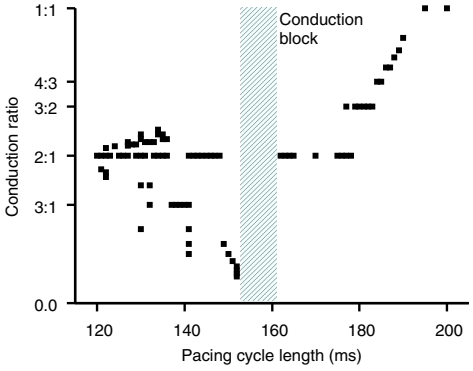

Fig. 3. Conduction ratio with various pacing rates. During higher pacing rates, intermittent conductions in the AV node were observed except for the pacing cycle lengths between 153 and 161 ms in which AV conduction block occurred.

Fig. 5 shows the recovery and refractory curves. The recovery curve built during the premature stimuli at different coupling intervals, S1–S2. The conduction time was the interval between the two activation times recorded from the atrial and nodal-His cells. The refractory curve shows the relationships between the S1–S2 interval and the H1–H2 interval corresponding to the R–R interval in the electrocardiogram.

The discontinuity in the recovery and refractory curves reflects the shift of the conduction pathway from the fast pathway with a long refractory period to the slow pathway with a short refractory period.

C. Ventricular rate control during atrial fibrillation

During AF, the activity within the fast and slow pathways was irregular, and local conduction blocks occurred frequently. Consequently, the average frequency of the action potentials reaching the bundle of His was decreased compared with the atrial cells (Fig. 6 A).

1) Effects of digitalis: Elevated intracellular Na^+ concentration reduces the transmembrane Na^+ gradient, which

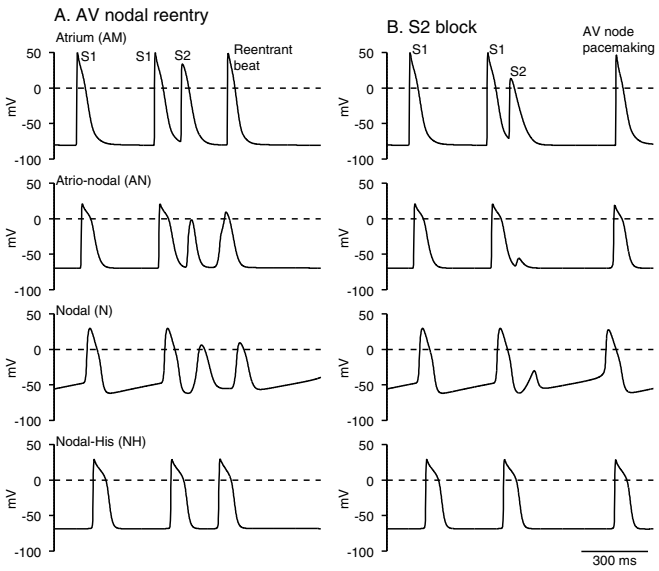

Fig. 4. Effects of premature stimulus on AV nodal conduction.

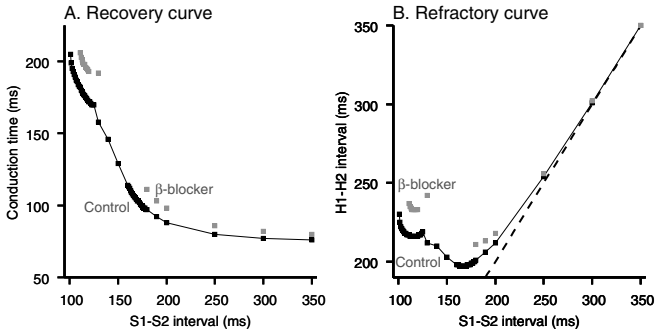

Fig. 5. Recovery and refractory curves of the AV node. Effects of beta-blockers on these curves are also shown.

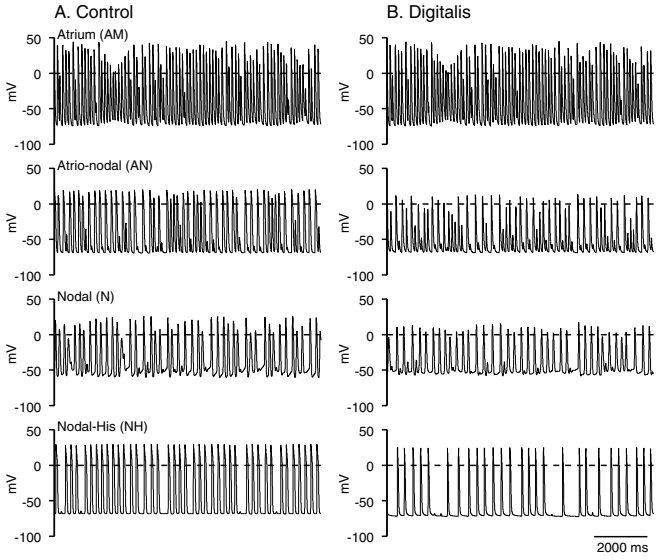

Fig. 6. AV nodal conduction during AF in the control (A) and after application of digitalis (B).

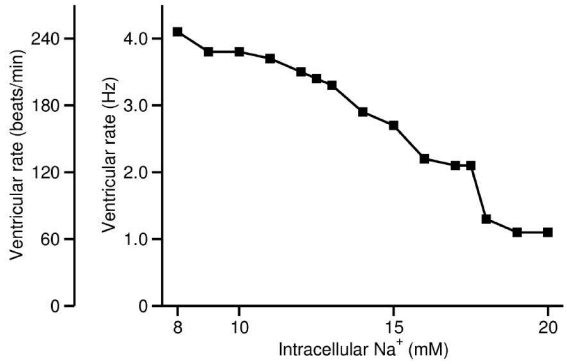

Fig. 7. Effects of digitalis on the ventricular rate during AF.

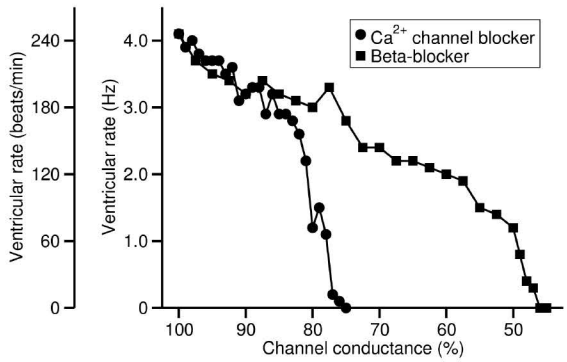

Fig. 8. Effects of Ca^{2+} channel blockers and beta-blockers on the ventricular rate during AF.

results in a decreased action potential upstroke and slowed action potential conduction (Fig. 6 B). Na^{+}-overload also shortened the action potential duration in the AV node. Consequently, the ventricular rate was decreased at high concentrations of Na^{+} (Fig. 7).

Because of the differential sensitivity of the cardiac conduction system and working myocardium to the toxic effects of digitalis, conduction blocks may occur most readily in the cardiac conduction system such as the AV node.

2) Effects of Ca^{2+} *channel blockers:* After partial block of $I_{Ca,L}$, conduction block occurred in the AV node as a result of the decreasing excitation rate in the nodal–His cell corresponding to the ventricular rate (Fig. 8).

3) Effects of beta-blockers: Beta-blockers can also control the ventrirular rate during AF (Fig. 8). The mechanisms may include slowing of AV nodal conduction, which is associated with increases in the conduction time and the AV nodal effective refractory period (Fig. 5 B)

4) Effects of fast pathway ablation: Conduction properties of the AV nodal pathways were determined before and after fast or slow pathway ablation. Elimination of the fast pathway reduced the ventricular rate during AF. Fast pathway ablation allowed slow pathway conduction, which slowed the ventricular rate during AF. Slow pathway ablation exhibited a minor effect on the ventricular rate. Fast pathway ablation results in elimination of the fast pathway, and the remaining slow pathway limits AV nodal conduction due to slow conduction. However, slow pathway ablation may not sufficiently control of the ventricular rate during AF.

IV. Conclusion

In this study, we have modified a one-dimensional multicellular model including two conduction pathways from the right atrium to the bundle of His through the AV node for rabbits. Using this model, we simulated several phenomena on the AV node such as AV nodal reentry and ventricular rate control during AF. Although some of the simulation results did not match previous simulation results [12], our model simulated a wide range of findings observed experimentally on the application of digitalis, ionic channel blockers and beta-blockers. The broad agreement between the experimental and theoretical findings suggests that the model and the explanations of the action of digitalis may be correct. Our simulation results suggest that the dual conduction pathway in the AV node is important in AV nodal conduction. Our model also increases the understanding of the complex phenomena in the AV node.

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