# Heart block in the athlete – role of ion channel remodelling as studied using a one-dimensional computational model of the atrioventricular node

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## Abstract

*In swim-trained mice, we previously observed atrioventricular (AV) node dysfunction characterised by first-degree heart block and a prolonged Wenckebach cycle length. This was concomitant with diffuse transcriptional, protein and functional remodelling of the hyperpolarization-activated cyclic nucleotide–gated (HCN) and L-type $Ca^{2+}$ channels known to be involved in AV node action potential generation and conduction. Notably, patch clamp recordings from isolated AV node myocytes demonstrated a significant reduction of $I_f$ (by ~60%) and $I_{Ca,L}$ (by ~40%) in swim-trained mice as compared to sedentary control mice. The effect of the observed changes in ionic currents was investigated using a one-dimensional computational model of the AV node made up of 100 AV node elements, each 100 μM in length. This was used in conjunction with a biophysically-detailed model of the rabbit AV node action potential. On decreasing $I_f$ by ~60% and $I_{Ca,L}$ by ~40% to mimic the effect of athletic training, the conduction velocity of the AV node model was reduced by 25% from 9.5 to 7.1 cm/s. The reduction was solely the result of the decrease in $I_{Ca,L}$. The decrease in $I_f$ (modelled in the conventional way as a time-dependent hyperpolarization-activated inward current) had no effect on the conduction velocity, despite experimental evidence that $I_f$ can affect AV node conduction. However, if the model of $I_f$ was modified to incorporate an instantaneous current, the decrease in $I_f$ also contributed to the reduction in the conduction velocity. We conclude that ionic remodelling of the AV node is a key mechanism underlying heart block in the athlete.*

## 1. Introduction

First- and second-degree heart block, resulting from slower conduction of the action potential through the atrioventricular (AV) node, is common in athletes and has been correlated to the intensity and length of training [1]. In athletes, bradyarrythmias resulting from dysfunction of the cardiac conduction system (including the AV node) can result in syncope [2].

In swim-trained mice, AV node dysfunction characterised by first-degree heart block and a prolonged Wenckebach cycle length have been observed previously [3]. This was concomitant with diffuse transcriptional, protein and functional remodelling of the hyperpolarization-activated cyclic nucleotide–gated (HCN) and L-type $Ca^{2+}$ channels known to be involved in AV node action potential generation and conduction [3].

In this study, the effect of the observed changes in ionic currents on AV node conduction was investigated using a one-dimensional computational model of the AV node. This was used in conjunction with a biophysically-detailed model of the rabbit AV node action potential [4]. The model of $I_f$ in the AV node action potential model was also modified to incorporate an instantaneous current as suggested by Proenza *et al*. [5].

## 2. Methods

To simulate the AV node action potential, the model of the rabbit AV node action potential (N-type) from Inada *et al.* [4] was used. General equations are:

$$\frac{dV}{dt} = -\frac{I_{total}}{C_m} \quad (1)$$

$$I_{total} = I_{Ca,L} + I_{K,r} + I_f + I_{st} + I_p + I_{NaCa} + I_b \quad (2)$$

where $V$ (mV) is the membrane potential, $t$ (ms) is the time, $I_{total}$ (pA) is the total membrane current, and $C_m$ (pF) is the membrane capacitance. The total membrane current is the sum of seven ionic currents, which are shown in equation (2).

A one-dimensional (1D) model was used to simulate conduction in the AV node. The model includes 100

elements and each element is 100 μm in length. The reaction-diffusion equation was used:

$$\frac{\partial V}{\partial t} = -\frac{I_{total}}{C_m} + D\frac{\partial^2 V}{\partial x^2} \qquad (3)$$

where $D$ is the diffusion coefficient. $D$ was set to 0.001 μS mm$^2$.

One end of the model (elements 1 to 3) was stimulated at 3 Hz. The conduction velocity was calculated from the times of arrival of the action potential at the 41$^{th}$ and 61$^{th}$ elements to avoid the influence of the boundaries.

Patch clamp recordings from isolated AV node myocytes demonstrated a significant reduction of $I_f$ (by ~60%) and $I_{Ca,L}$ (by ~40%) in swim-trained mice as compared to sedentary control mice. The measured current-voltage ($I$-$V$) relationships of $I_{Ca,L}$ and $I_f$ are shown in Figure 1C,D. To simulate the effect of athletic training, the conductance of $I_f$ in the model was reduced by 60% and the conductance of $I_{Ca,L}$ in the model was reduced by 40%. The simulated $I$-$V$ relationships of $I_{Ca,L}$ and $I_f$ are shown in Figure 1A,B.

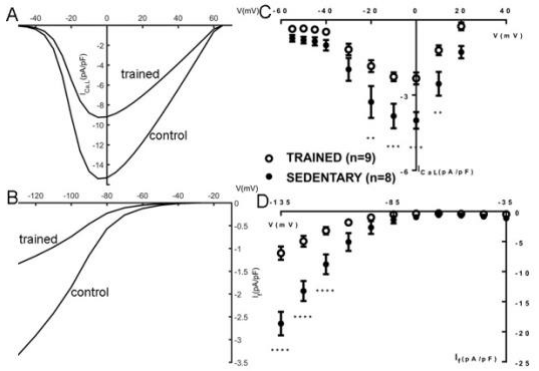


Figure 1 A and B, simulated $I$-$V$ relationships of $I_{Ca,L}$ (A) and $I_f$ (B) in control and trained AV node cells. C and D, measured $I$-$V$ relationships of $I_{Ca,L}$ (C) and $I_f$ (D) in control and trained AV node cells.

## 2.1. Simulation of AV node conduction using original AV node (N type) model

The effect of exercise training on AV node conduction was simulated based on the data in Figure 1A,B. Results shows that the conduction velocity of the AV node action potential was reduced by 25% from 9.5 to 7.1 cm/s, as shown in Figure 2A,B. Figure 2C shows the time course of $I_f$ and $I_{Ca,L}$ during the action potential in the control and trained conditions in the computer simulation. The slowing of the conduction velocity was primarily the result of the reduction in $I_{Ca,L}$: decreasing $I_f$ alone resulted in a reduction in the conduction velocity of 0.85% and decreasing $I_{Ca,L}$ alone resulted in a reduction in the conduction velocity of 24%. The lack of effect of $I_f$ is consistent with our earlier simulations [8], but it is inconsistent with experimental data showing that $I_f$ does influence AV node conduction [6-7].

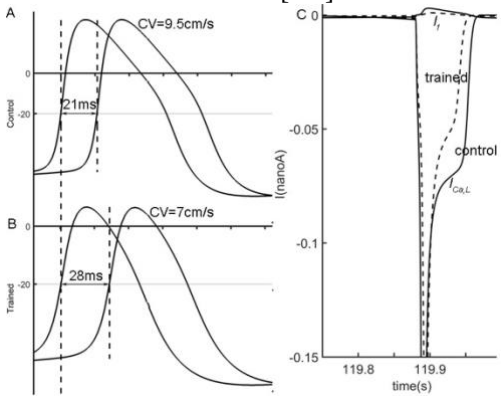


Figure 2 Simulations of effect of athletic training. A: action potential recorded from 41$^{th}$ and 61$^{th}$ elements of the 1D model of the control (A) and trained (B) AV node. C, $I_f$ and $I_{Ca,L}$ in control (solid line) and trained (dashed line) AV node cells.

## 2.2. Instantaneous component of $I_f$

In the case of HCN2, there is evidence that there is an instantaneous ($I_{inst}$) component of $I_f$ as well as a time-dependent component ($I_h$) of $I_f$ from Proenza *et al.* [5]. Figure 3 (Figure 1C in [5]) shows the correlation between $I_{inst}$ and $I_h$ amplitudes. A Pearson correlation revealed a significant positive covariation between these amplitudes (slope = 0.16, $P$ = 0.003, $r$ = 0.25). These observations suggested that the same process governs production of $I_h$ and $I_{inst}$, and that both currents may flow through the same channel [5].

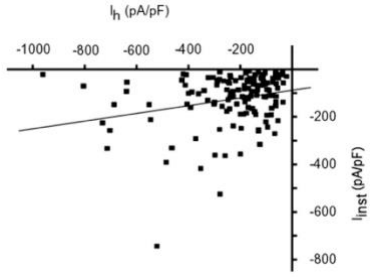


Figure 3 Correlation between $I_{inst}$ and $I_h$ amplitudes. $I_{inst}$ density is plotted as a function of $I_h$ density in the same cells ($n$ = 138) in response to voltage steps to −150 mV. The line is a linear fit of the data and indicates a positive covariance ($P$ = 0.003) between $I_{inst}$ and $I_h$. From Proenza *et al.* [5].

The electrophysiological properties of HCN4 expressed in COS-7 cells were examined by Ishii *et al.* [9]. Figure 4A shows representative current traces of HCN4 current ($I_f$) from their study. Figure 4B shows $I$-$V$ relationships. The closed circles indicate the amplitude of the instantaneous current measured at the beginning of hyperpolarizing pulses. The open circles indicate the amplitude of $I_f$ measured at the end of pulses. The

similarity of the two *I-V* relationships suggests both currents flow through the same channel

At present, no $I_f$ model includes an instantaneous component.

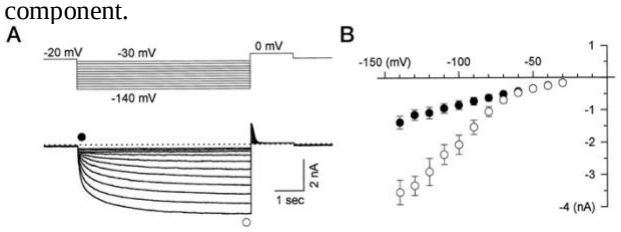


Figure 4 Voltage-dependent gating of HCN4. A, representative current recordings of the HCN4 current ($I_f$). The initial current ($I_{inst}$) and the steady-state current ($I_f$) were measured at the times indicated (● and ○, respectively). *B*, *I-V* relationships of $I_{inst}$ and $I_f$. From Ishii *et al.* [9].

## 2.3. Modification of $I_f$ to incorporate an instantaneous current ($I_{inst}$)

To incorporate an instantaneous current, $I_{inst}$, three parameters must be determined, the reversal potentials for $I_{inst}$ and $I_h$, the *I-V* relationship of $I_{inst}$, and the correlation between $I_{inst}$ and $I_h$.

According to Proenza *et al.* [5], the reversal potentials for $I_{inst}$ and $I_h$ do not differ significantly. Hence, the reversal potentials for $I_{inst}$ and $I_h$ were set to be the same as the reversal potential for $I_f$ in Inada's original AV node model (-30 mV). Based on the *I-V* relationship of $I_{inst}$ (shown in Figure 4B) measured by Ishii *et al.* [9], a linear *I-V* relationship of $I_{inst}$ was used. According to the results from Proenza *et al.* [5] (Figure 3) and Ishii *et al.* [9] (Figure 4B), the ratio of $I_{inst}$ to $I_h$ varies from ~0.3 to ~1.

Let $I_f = I_{inst} + I_h$.

The model *of* $I_h$ was set as the original model of $I_f$, shown in equation (4):

$$\begin{aligned} y_\infty &= \frac{1}{1+\exp((V-V_{1/2})/k)} \\ \tau_y &= 0.25 + 2.0\exp(-(V-(-70))^2/500) \\ \frac{dy}{dt} &= \frac{y_\infty - y}{\tau_y} \\ I_h &= g_h y (V - E_f) \end{aligned} \quad (4)$$

where $y$ is the activation variable of $I_h$, $y_\infty$ is the voltage-dependent steady-state value of $y$, $\tau_y$ is the voltage-dependent time constant of $y$, $V_{1/2}$ is the voltage at which half activation occurs, and $k$ is a factor determining how steeply the activation curve changes with voltage. $g_h$ is conductance of $I_h$.

The *I-V* relationship of $I_{inst}$ was set to be linear [9]. The model of $I_{inst}$ is:

$$I_{inst} = g_{inst}(V - E_f) \quad (5)$$

where $g_{inst}$ is the conductance of $I_{inst}$.

To obtain the same action potential shape and the same spontaneous cycle length, on adding an instantaneous component of $I_f$, equivalent background current was subtracted.

$$I_b = g_b(V - E_b) \quad (6)$$

where $g_b$ is conductance of $I_b$ and $E_b$ is the reversal potential for $I_b$.

The ratio of instantaneous to time-dependent components, $g_{inst}/g_h$, was set to 0.3, 0.5 and 1 to exam the effect of $I_f$ on AV node conduction. Table 1 shows modified parameters of $I_b$ with $g_{inst}/g_h$=0.3, 0.5 and 1. Figure 5 shows simulated traces of $I_f$ incorporating an instantaneous component (from a single AV node cell) with $g_{inst}/g_h$=0.3, 0.5 and 1. The bottom set of traces ($g_{inst}/g_h$=1) roughly match the traces shown in Figure 4A.

Table 1 Matching $I_b$ to $g_{inst}/g_h$

| $g_{inst}/g_h$ | 0 | 0.3 | 0.5 | 1 |
|---|---|---|---|---|
| $g_b$(μS) | 0.0012 | 0.0009 | 0.0007 | 0.0002 |
| $E_b$(mV) | -22.5 | -20 | -17 | 15 |

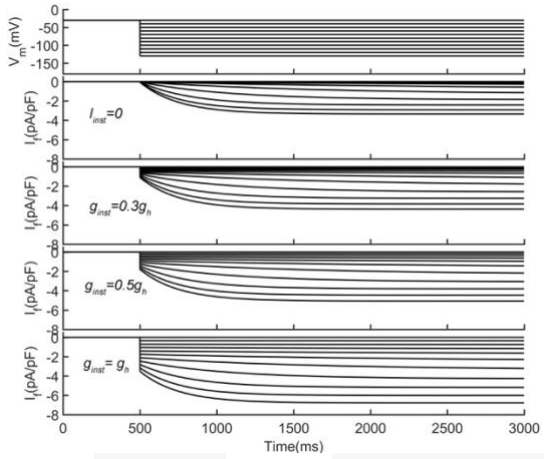


Figure 5 Simulated traces of $I_f$ incorporating an instantaneous component (from a single AV node cell). The ratio of instantaneous to time-dependent components, $g_{inst}/g_h$=0.3, 0.5 and 1.

# 3. Results

## 3.1. Effect of $I_f$ on AV node conduction and AV node pacemaking

Incorporating an instantaneous current, $I_{inst}$ ($g_{inst}/g_h$=0.3, 0.5 and 1), significantly increases $I_f$ in single cell simulations (Figure 6A). The effect of $I_f$ on AV node conduction was calculated using the 1D model. Figure 6B shows that blocking $I_f$ decreases AV node conduction velocity (CV) and the decrease in CV increases from 0.85% to 18.5% as $g_{inst}/g_h$ increases (from 0 to 100%).

Table 2 Effect of the instantaneous component of $I_f$ on AV node pacemaking.

| | $g_{inst}/g_h$ | CL (ms) | Change |
|---|---|---|---|
| Control | 0 | 462 | -- |
| No $I_f$ | 0 | 471 | 1.88% |
| | 0.3 | 528 | 14.2% |
| | 0.5 | 581 | 25.7% |
| | 0.7 | 671 | 45.2% |
| | 0.9 | 1023 | 121.4% |
| | 1 | ∞ | ∞ |

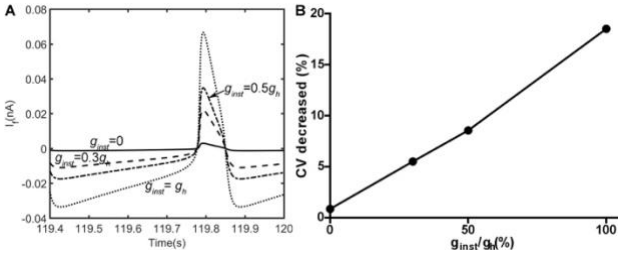


Figure 6 A, traces of $I_f$ during the spontaneous AV node action potential when $g_{inst}/g_h$=0.3, 0.5 and 1. B, decrease in AV node conduction velocity on blocking $I_f$ after incorporation of an instantaneous component of $I_f$.

A single AV node cell model was used to simulate the effect of $I_f$ on AV node pacemaking. Liu *et al.* [10] reported that blocking $I_f$ increases the spontaneous cycle length of the AV node (by ~73.56%). Table 2 shows that CL increases as $g_{inst}/g_h$ increases after blocking $I_f$. It shows that $g_{inst}/g_h$ should be more than 0.7 to represent the experiment.

## 3.2. Effect of athletic training on AV node conduction and pacemaker activity

Table 3 Exercise training is predicted to affect the pacemaker activity of the AV node.

| | $g_{inst}/g_h$ | CL (ms) | Changes |
|---|---|---|---|
| Control | 0 | 462 | -- |
| 40%$I_f$ + 60%$I_{CaL}$ | 0 | 524 | 13.4% |
| | 0.3 | 568 | 22.9% |
| | 0.5 | 603 | 30.5% |
| | 0.7 | 646 | 39.8% |
| | 0.9 | 762 | 64.8% |
| | 1 | 746 | 61.4% |

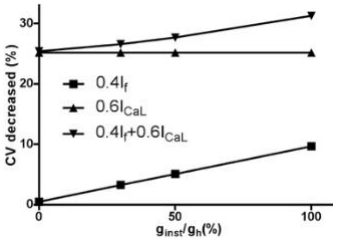


Figure 7 Decrease in AVN conduction velocity caused by exercise training with different patterns of ion channel remodelling.

To simulate the effect of athletic training on AV node conduction and spontaneous cycle length, 0.4$g_h$ and 0.6 $g_{Ca,L}$ were used. The results shows that the reduction of $I_f$ and $I_{Ca,L}$ significantly slowed AV conduction (Figure 7) and increased the spontaneous cycle length of the AV node (Table 3).

## 4. Conclusion

We conclude that ionic remodelling of the AV node is a key mechanism underlying heart block in the athlete.

## Acknowledgements

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