

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. 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. 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, bradyarrhythmias 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:

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

where D is the diffusion coefficient. D was set to 0.001 $\mu\text{S mm}^2$.

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 41th and 61th 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.

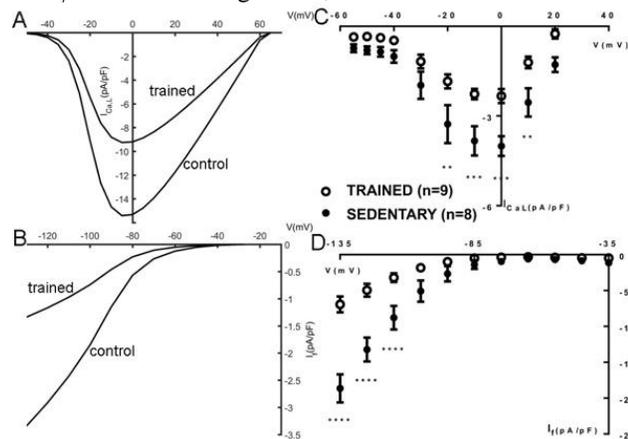


Figure 1. A and B, simulated I - V relationships of $I_{Ca,L}$ (A) and I_f (B) in control and trained AV node cells. C and D, measured I - V relationships of $I_{Ca,L}$ (C) and I_f (D) in control and trained AV node cells.

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].

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].

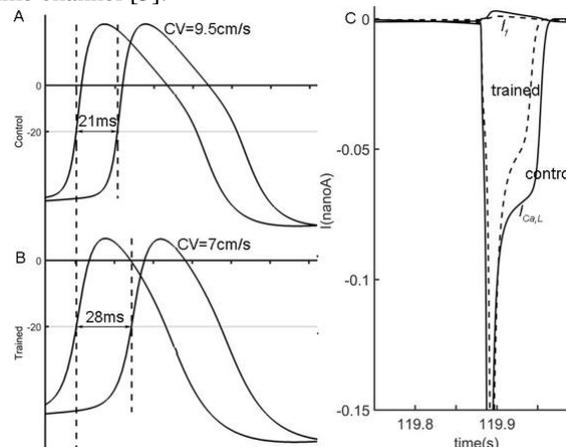


Figure 2. Simulations of effect of athletic training. A: action potential recorded from 41th and 61th elements of the 1D model of the control (A) and trained (B) AV node. C, I_f and $I_{Ca,L}$ in control (solid line) and trained (dashed line) AV node cells.

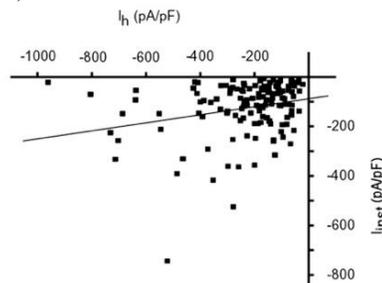


Figure 3. Correlation between I_{inst} and I_h amplitudes. I_{inst} density is plotted as a function of I_h density in the same cells ($n = 138$) in response to voltage steps to -150 mV. The line is a linear fit of the data and indicates a positive covariance ($P = 0.003$) between I_{inst} and I_h .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

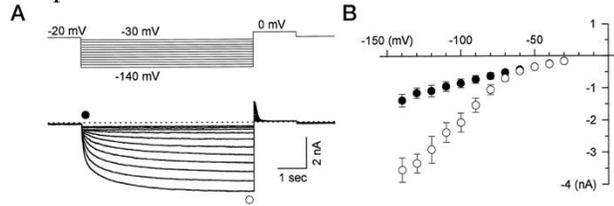


Figure 4. Voltage-dependent gating of HCN4. A, representative current recordings of the HCN4 current (I_f). The initial current (I_{inst}) and the steady-state current (I_f) were measured at the times indicated (\bullet and \circ , respectively). B, I - V relationships of I_{inst} and I_f . From Ishii *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):

$$y_\infty = \frac{1}{1 + \exp((V - V_{1/2})/k)}$$

$$\tau_y = 0.25 + 2.0 \exp(-(V - (-70))^2 / 500)$$

$$\frac{dy}{dt} = \frac{y_\infty - y}{\tau_y}$$

$$I_h = g_h y (V - E_f) \quad (4)$$

where y is the activation variable of I_h , y_∞ is the voltage-dependent steady-state value of y , τ_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:

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

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_b , 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 $g_{inst}/g_b=0.3, 0.5$ and 1. Figure 5 shows simulated traces of I_f incorporating an instantaneous component (from a single AV node cell) with $g_{inst}/g_b=0.3, 0.5$ and 1. The bottom set of traces ($g_{inst}/g_b=1$) roughly match the traces shown in Figure 4A.

Table 1 Matching I_b to g_{inst}/g_b

g_{inst}/g_b	0	0.3	0.5	1
g_b (μ S)	0.0012	0.0009	0.0007	0.0002
E_b (mV)	-22.5	-20	-17	15

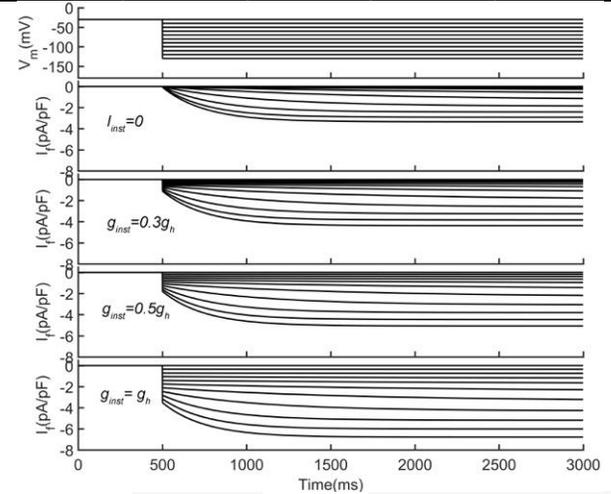


Figure 5. Simulated traces of I_f incorporating an instantaneous component (from a single AV node cell). The ratio of instantaneous to time-dependent components, $g_{inst}/g_b=0.3, 0.5$ and 1.

3. Results

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

Incorporating an instantaneous current, I_{inst} ($g_{inst}/g_b=0.3, 0.5$ 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_b increases (from 0 to 100%).

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.

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	∞	∞

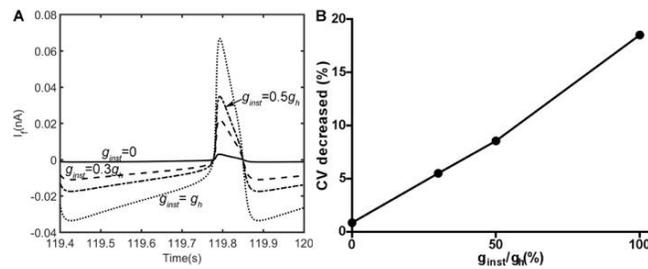


Figure 6. A, traces of I_f during the spontaneous AV node action potential when $g_{inst}/g_h=0.3, 0.5$ and 1 . B, decrease in AV node conduction velocity on blocking I_f after incorporation of an instantaneous component of I_f .

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%

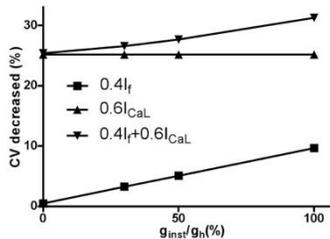


Figure 7. Decrease in AVN conduction velocity caused by exercise training with different patterns of ion channel remodeling.

To simulate the effect of athletic training on AV node conduction and spontaneous cycle length, $0.4g_h$ and $0.6g_{CaL}$ were used. The results shows that the reduction of I_f

and I_{CaL} 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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