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Mathematical Simulation of Slowing of Cardiac Conduction Velocity by Elevated Extracellular $[K^+]$ in a Human Atrial Strand

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Abstract—We have studied the dependence of conduction velocity (θ) on extracellular potassium concentration ($[K^+]_o$) in a model of one-dimensional conduction using an idealized strand of human atrial cells. Elevated $[K^+]_o$ in the 5–20 mM range shifts the resting potential (V_{rest}) in the depolarizing direction and reduces input resistance (R_{in}) by increasing an inwardly rectifying K^+ conductance, I_{Kl}. Our results show that in this model: (1) θ depends on $[K^+]_o$ in a ''biphasic'' fashion. Moderate elevations of $[K^+]_o$ (to less than 8 mM) result in a small increase in θ, whereas at higher $[K^+]_o$ (8–16 mM) θ is reduced. (2) This biphasic relationship can be attributed to the competing effects of (i) the smaller depolarization needed to reach the excitation threshold ($V_{thresh}-V_{rest}$) and (ii) reduced availability (increased inactivation) of sodium current, I_{Na}, as the cell depolarizes progressively. (3) Decreasing R_{in} reduces θ due to the increased electrical load on surrounding cells. (4) The effect on θ of $[K^+]_o$-induced changes in R_{in} in the atrium (as well as other high-R_{in} tissue, such as that of the Purkinje system or nodes) is likely to be small. This effect could be substantial, however, under conditions in which R_{in} is comparable in size to gap junction resistance and membrane resistance (inverse slope of the whole-cell current–voltage relationship) when sodium channels are open, which is likely to be the case in ventricular tissue. © *2000 Biomedical Engineering Society.* [S0090-6964(00)00308-8]

Keywords—Action potential conduction, Computer modeling, Inward rectification, Cable equations, Hyperkalemia, Ischemia.

INTRODUCTION

Elevation of extracellular potassium concentration, $[K^+]_o$, begins to occur almost immediately upon coronary occlusion, and may rise as high as 15–20 mM within 10–20 min.[6] Although the effects of ischemia include other conditions such as acidosis and anoxia, elevated $[K^+]_o$ is believed to be the major cause of conduction slowing in early ischemia.[12] Moreover, vigorous exercise can rapidly raise plasma K^+ levels to 8–9 mM,[10] subjecting the heart to nearly double the normal $[K^+]_o$. The effects on cellular electrophysiology of increased $[K^+]_o$ include a depolarizing shift in the resting potential (V_{rest}) as well as a decrease in the input resistance (R_{in}) of cardiac cells due to an increased conductance of the inward rectifier K^+ current, I_{Kl}.[16] Resting potential and input resistance, along with the intercellular coupling resistance, have been shown to be important factors in determining the electrotonic interactions between electrically connected cell pairs.[14] Experiments carried out by Wagner *et al.*[15] in which a model SA node cell was electrically coupled to a real isolated ventricular cell demonstrated that the range of coupling conductances for which the SA node cell was able to drive the ventricular cell is modulated by $[K^+]_o$. These authors concluded that a combination of reduced R_{in} and elevated excitation threshold (V_{thresh}) (both due to the effects of $[K^+]_o$ on the inwardly rectifying K^+ current, I_{Kl}) could explain why a larger coupling conductance is necessary when the ventricular cell is subject to high $[K^+]_o$.

In multicellular preparations, it has been observed that gradually increased $[K^+]_o$ results in a ''biphasic'' response in conduction velocity (θ). Moderate increases in $[K^+]_o$ result in increased θ (''supernormal conduction'') whereas larger increases lead to conduction slowing.[1,4,12] Depolarization of V_{rest} and reduced R_{in} in the presence of elevated $[K^+]_o$ would both be expected to reduce θ due to reduced availability of I_{Na} at rest and increased electrical load on surrounding cells (the amount of current that one cell must supply to depolarize another is increased), respectively. However, it has been suggested that under some circumstances depolarization of V_{rest} might increase excitability since V_{rest} is brought closer to the threshold of excitation, V_{thresh}.[1] For small depolarizations of V_{rest} this effect may be greater than the effect of reduced I_{Na} availability, which may explain the region of supernormal conduction for modest increases in $[K^+]_o$.[1]

As outlined above, conduction velocity (as well as the success or failure of conduction) depends critically on subthreshold properties of cardiac cells. A complex interplay between factors such as I_{Na} availability, excita-

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tion threshold, and input resistance determines the coupling between adjacent cells in cardiac tissue. Atrial and ventricular cells are known to have very different subthreshold properties.[3,16] This is particularly true for the input resistance, R_{in}, which is primarily determined by the slope of I_{Kl} under resting and diastolic conditions. Since I_{Kl} is much smaller in atrial than in ventricular cells,[2,3,16] the R_{in} of ventricular cells is much smaller than that of atrial cells. Whalley *et al.*[16] compared the reduction of the maximum rate of rise of the action potential, $(dV/dt)_{max}$, due to elevated $[K^+]_o$ in guinea pig atrial and ventricular isolated myocytes. In atrial cells, they found that $(dV/dt)_{max}$ was a function of I_{Na} availability at rest, i.e., a function of the resting membrane potential, V_{rest}. In ventricular cells, however, they reported a ''voltage-independent'' effect on $(dV/dt)_{max}$ that could not be explained in terms of I_{Na} availability and V_{rest}. The observation that Ba^{2+} abolished this effect led these authors to the conclusion that it was related to the larger I_{Kl} in ventricular cells.

In this study, we have investigated the influence of I_{Na} availability, excitation threshold, and R_{in} on the $[K^+]_o$-dependence of conduction velocity in a computational model of an idealized strand of human atrial cells.[8,9] Using this approach, the effects of elevated $[K^+]_o$ on R_{in} can be separated from the effects related to I_{Na} and excitation threshold, allowing the influence of each to be studied separately. Furthermore, it is of interest to extrapolate these results to lower values of R_{in}, corresponding to ventricular cells, to compare the relative importance of R_{in} in ventricular cells to that in atrial cells.

METHODS

Simulations were carried out for an idealized cardiac strand model consisting of 30 human atrial cells. Figure 1(A) shows the electrical equivalent circuit for a patch of the cell membrane. The descriptions of ion channel currents in our previously published model of a single human atrial cell[8] were used, except that the maximum permeability parameter of I_{Na} had to be increased by a factor 3.19 to reach a desired nominal conduction velocity of 60 cm/s. Figure 1(B) shows the geometry of the model, consisting of two concentric cylinders. The innermost cylinder represents the human atrial cells, which are assumed to be right cylinders of length 130 μm and diameter 11 μm. The cells are arranged end to end and coupled by gap junctions. Our model treats the strand of cells as a continuum, in which the gap junctions appear as regions of lower axial conductivity at the interface between cells. The outermost cylinder in the model represents the barrier formed by connective tissue and surrounding cells and forms a ''cleft space'' surrounding each cell as in the single-cell model. Since all ion concentrations are fixed in the simulations presented in this article, the effect of the cleft space is simply to introduce an extracellular resistance in the model.

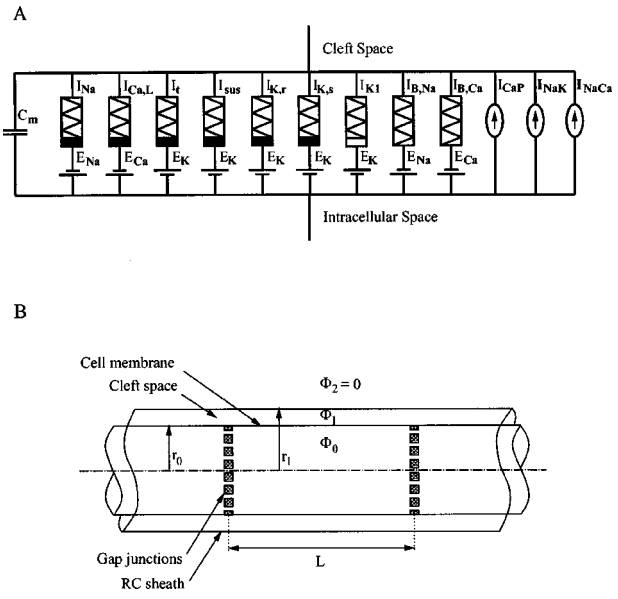

FIGURE 1. Schematic of the human atrial strand model used in this article. (A) Equivalent circuit for the electrical properties of the atrial cell membrane (sarcolemma). (B) Geometry of the idealized human atrial strand. The cells are assumed to be 130 μm long and 11 μm in diameter. Each cell is divided into ten segments.

The numerical method used to simulate propagation in this model is our general approach described elsewhere,[9] reduced to the case of fixed ion concentrations. Briefly, the equations governing propagation are

$$\begin{cases} 2r_o C_o \dfrac{\partial \Phi_o}{\partial t} = -2r_o J_o + r_0^2 \dfrac{\partial}{\partial x}\left(\sigma_o \dfrac{\partial \Phi_o}{\partial x}\right) + 2r_1 C_1 \dfrac{\partial \Phi_1}{\partial t} \\ (2r_1 C_1 + 2r_o C_o)\dfrac{\partial \Phi_1}{\partial t} = -2r_1 J_1 + 2r_o J_o + (r_1^2 - r_0^2)\dfrac{\partial}{\partial x}\left(\sigma_1 \dfrac{\partial \Phi_1}{\partial x}\right) + 2r_o C_o \dfrac{\partial \Phi_o}{\partial t}, \end{cases}$$

where C_i denotes the specific capacitance and r_i the radius of cylinder i, Φ_i the potential in volume i [see Fig. 1(B)], J_i the radial current density through membrane i (given by the membrane model), and σ_i is the conductivity of the medium in volume i. No-flux boundary conditions were employed. This continuous equation is discretized using a finite difference method where each cell is subdivided into equally sized segments. As described previously,[9] we employ the backward Euler method for the partial differential equations governing the potentials (above). The resulting set of simultaneous equations is solved at each time step using LU factorization followed by backsubstitution.[11] The ordinary differential equations for the membrane gating variables are solved using the explicit (forward) Euler method. We studied the dependence of the error in θ on the number of segments used[7] and found that ten segments per cell was sufficient to ensure an accurate θ under most conditions. The error in θ incurred by using a single segment per cell[12] was less than 1% at nominal intercellular coupling resistance, and increased to 5%–6% at ten times nominal resistance. For many purposes it will therefore be sufficient to use a single segment per cell. Nevertheless, in order to rule out any involvement of numerical errors, all simulations presented here used ten segments per cell. It was furthermore verified that the length of the model (30 cells) is sufficient to ensure that conduction at the center of the model is unaffected by ''end effects,'' i.e., that the conduction velocity does not change if more cells are added to the model. The values for θ reported in this article are measured as an average across six cells located at the center of the model.

RESULTS

Effects of Elevated $[K^+]_o$ *on* θ

Figure 2 shows simulated conduction velocities for selected levels of $[K^+]_o$. There is a ''biphasic'' relationship between conduction velocity and $[K^+]_o$. Small increases in $[K^+]_o$ increase θ (''supernormal conduction''), whereas larger increases strongly reduce θ until conduction fails around 17 mM. The inset in Fig. 2 illustrates the dependence of the I_{Kl} current–voltage relationship on $[K^+]_o$. Note that the resting potential is depolarized, becoming closer to the threshold for I_{Na} activation, but at the expense of reduced availability of I_{Na} current. The slope of I_{Kl} is increased, i.e., the input resistance is reduced, which increases the electrical load that the cell presents to surrounding cells. Since it is unclear how these effects interact to result in a biphasic relation between θ and $[K^+]_o$, we attempted to separate the effects.

Influence of I_{Na} *Availability and Excitation Threshold*

As the resting potential is depolarized due to increased $[K^+]_o$, its location relative to the gating characteristics of I_{Na} is changed. A similar effect can be achieved without changing the input resistance of the cell by instead shifting the voltage dependence of the I_{Na} gating variables. Figure 3(A) shows how θ is affected by shifting the steady-state voltage dependence of the h gating variable, i.e., increasing or reducing the availability of I_{Na} current at rest. Clearly, this is an important parameter in determining θ. Similarly, Fig. 3(B) shows the effect on θ of shifting the steady-state voltage dependence of the m gating variable. Positive shifts in this parameter reduce θ by moving the threshold for excitation away from the resting potential. Large positive shifts in m (or negative shifts in h) cannot be simulated independently since this opens up a substantial I_{Na} ''window current'' and destabilizes the resting potential. However, it is clear that negative shifts in h and positive shifts in m both tend to decrease θ.

If m and h are both shifted by the same amount, it is possible to run simulations with a stable resting potential over a relatively wide range of shifts [Fig. 3(C)]. These results demonstrate that the θ-reducing effects of positive

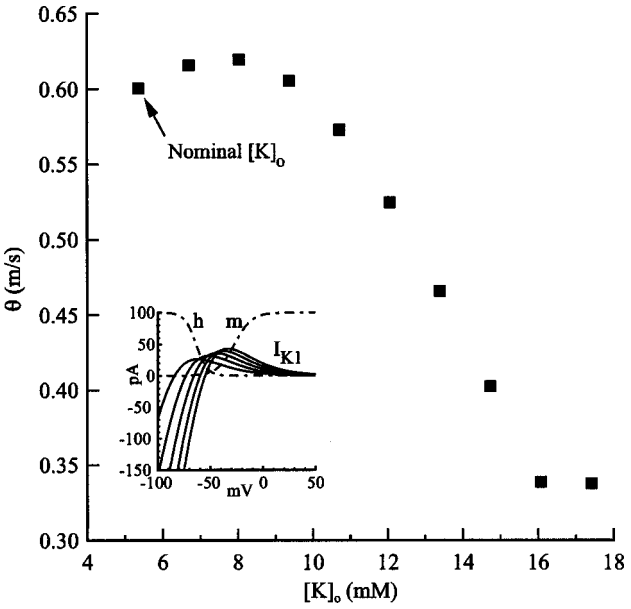

FIGURE 2. Dependence of conduction velocity on extracellular $[K^+]$. Note that with reference to a nominal conduction velocity (θ) of 60 cm/s at normal $[K^+]_o$=5.4 mM, θ is slightly increased for moderate $[K^+]_o$ elevation. After peaking around 8 mM, θ then gradually decreases, reaching a minimum value of approximately 33 cm/s. Conduction fails at $[K^+]_o$=17 mM. Inset: The current–voltage relation for the inward rectifier, I_{Kl}, is shifted in the depolarizing direction and the conductance increases as $[K^+]_o$ is raised. The result is a reduced distance to the excitation threshold ($V_{thresh}-V_{rest}$), reduced I_{Na} availability (h), and reduced R_{in}.

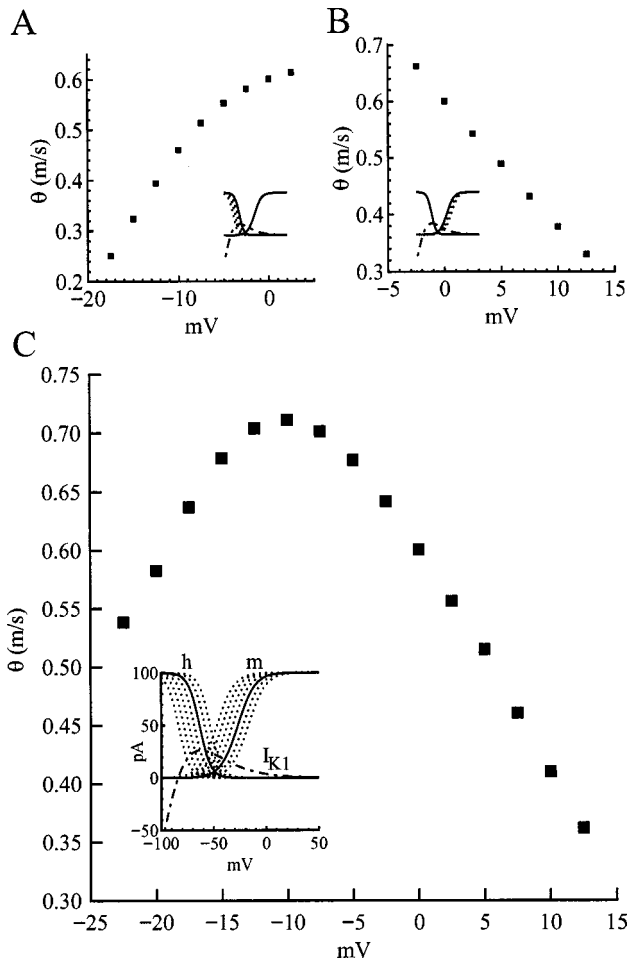

FIGURE 3. Effect on conduction velocity of shifting the voltage–dependence of I_{Na} gating. (A) The voltage-dependence of inactivation (*h*) controls the availability of I_{Na} current at V_{rest}. Reducing I_{Na} availability (hyperpolarizing shifts) reduces θ. (B) The voltage dependence of activation (*m*) controls the "distance" to threshold, $V_{thresh} - V_{rest}$. Increasing $V_{thresh} - V_{rest}$ (depolarizing shifts) reduces θ. (C) Results of simulations combining equal shifts in the gating variables *m* and *h*. Moderate hyperpolarizing shifts produce an increase in θ, whereas larger hyperpolarizing (and all depolarizing) shifts decrease θ. Note that a hyperpolarizing shift in I_{Na} gating reduces both $V_{thresh} - V_{rest}$ and I_{Na} availability, and thus approximates the effects of a depolarization of V_{rest} without changing R_{in}.

shifts in *m* dominate for positive shifts, and those of negative shifts in *h* dominate for large positive shifts. For small negative shifts, however, the response is biphasic in much the same way as the response to increased $[K^+]_o$ (Fig. 2). Notice that a negative shift moves V_{thresh} closer to V_{rest} and in that sense approximates the effects of a depolarization of V_{rest}. Small shifts result in an increase in θ, whereas larger shifts begin to reduce θ as the reduction in available I_{Na} becomes the dominant effect.

Influence of Input Resistance

To separate the effects on θ of reduced input resistance, R_{in}, at rest from those related to I_{Na} availability and excitation threshold, it was necessary to modify R_{in} without changing the resting potential. This was accomplished by simultaneous scaling and shift of the I_{Kl} formulation so that the I_{Kl} current at rest (and thus the resting potential itself) remained constant although the slope of I_{Kl} changed [see inset in Fig. 4(A)]. Figure 4(A) shows conduction velocity as a function of the slope of I_{Kl} at rest. The curve is relatively flat around the nominal value of I_{Kl} slope for the human atrial model. Given that the slope of I_{Kl} is approximately proportional to the square root of $[K^+]_o$, the relevant simulations will definitely be within the relatively flat portion of the curve. It appears, therefore, that $[K^+]_o$-induced changes in I_{Kl} slope would be of minor importance in determining θ in atrial tissue. For larger I_{Kl} slopes (i.e., for lower input resistance) the curve becomes steeper and for a cell with higher baseline I_{Kl}, slope changes in elevated $[K^+]_o$ could have a significant impact on θ. For comparison, the slope of I_{Kl} in the Luo–Rudy model (scaled to the size of the human atrial model) is indicated on the plot in Fig. 4(A).

DISCUSSION

We have studied the dependence of conduction velocity (θ) on extracellular K^+ concentration ($[K^+]_o$) using a model of one-dimensional conduction in a strand of human atrial cells. Moderate elevation of $[K^+]_o$, corresponding to what can occur during exercise,[10] causes a small increase in θ (Fig. 2), which peaks at approximately 8 mM. Above this peak, θ begins to decline and finally conduction fails at a $[K^+]_o$ of approximately 17 mM, i.e., within the range of $[K^+]_o$ that can occur during ischemia.[6] This "biphasic" dependence of θ on $[K^+]_o$ provides a potentially important safety factor for conduction, in that the conduction velocity remains approximately constant for all $[K^+]_o$ that can be expected to occur under normal physiological conditions. It is only at extreme values of $[K^+]_o$ that substantial conduction slowing occurs. The θ at the highest $[K^+]_o$ for which conduction is still maintained is approximately 33 cm/s, i.e., slightly more than half the nominal θ of 60 cm/s. The overall behavior of this model is consistent with the simulations reported by Shaw and Rudy[12] using the Luo–Rudy (LR) guinea pig ventricular model, as well as with the experimental results of Kagiyama *et al.*[4] Specifically, the range of $[K^+]_o$ resulting in supernormal θ (peaking around 8 mM) and the region of decrease are virtually identical to the results of Shaw and Rudy. However, whereas conduction failure occurs at similar $[K^+]_o$ levels, the degree to which θ is suppressed prior to this

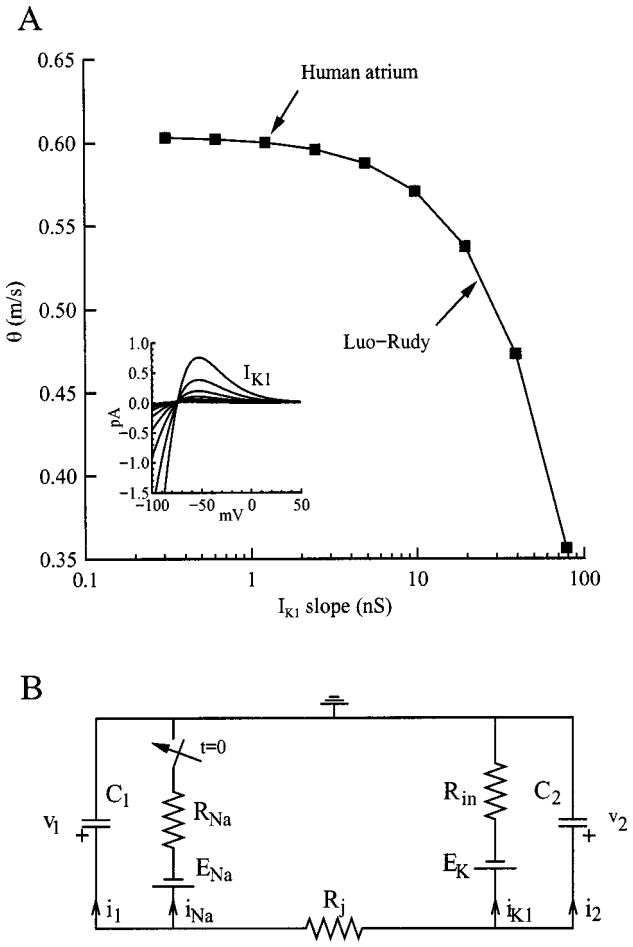

FIGURE 4. (A) Effect on conduction velocity of changing the slope of I_{Kl} at the resting potential. Changes within the range relevant to the human atrium (i.e., within ± a factor of 2 of nominal, see text) have minimal effects on θ. Changes in I_{Kl} slope around the nominal value for the Luo–Rudy ventricular model (scaled to the size of the human atrial model) result in larger changes in θ. (B) Simplified equivalent circuit for one cell (cell 1) coupled to a second (cell 2). R_j represents the coupling resistance of the gap junctions connecting the two cells. R_{Na} represents the membrane resistance (inverse slope of the whole-cell current–voltage relationship) when Na^+ channels are open. As the switch is closed (I_{Na} activates), E_{Na} in cell 1 attempts to charge its own capacitance (C_1) as well as, through the gap junction resistance R_j, that of cell 2 (C_2). This charging is opposed by the "shunt" consisting of R_{in} and E_K (representing I_{Kl}) in cell 2. If R_{in} is much larger than R_{Na} and R_j, coupling is maximally efficient and the exact value of R_{in} is of little importance.

point is much greater in the LR model. The lowest θ in the LR model is approximately 15 cm/s compared to 33 cm/s in our results. The nominal "normal" θ is 60 cm/s in both cases.

We hypothesized that the reason for this difference could be related to the differences in subthreshold properties between the two models (and between atrial and ventricular cells in general, as discussed in the Introduction). Elevated $[K^+]_o$ shifts the resting potential in the depolarizing direction and increases I_{Kl} conductance, which results in: (1) reduced "distance" from the resting potential to the excitation threshold, $V_{thresh}-V_{rest}$; (2) reduced availability of I_{Na} at V_{rest}; and (3) reduced R_{in} of the cell. Effect (1) tends to increase θ by increasing excitability, whereas (2) and (3) reduce θ by reducing excitability and increasing the electrical load on surrounding cells, respectively.

The most obvious difference in the (subthreshold) electrophysiological properties of atrial and ventricular cells is the size of I_{Kl}. It has previously been shown in multicellular preparations[5] and in single cells[16] that the effects of increased $[K^+]_o$ in atrial cells are fundamentally different from that in ventricular cells. In atrial cells, elevated $[K^+]_o$ produces a reduction in maximal rate of rise, $(dV/dt)_{max}$, which can be fully explained in terms of the reduced availability of I_{Na} resulting from depolarization of V_{rest}. In ventricular cells, however, $(dV/dt)_{max}$ is reduced considerably more than can be explained by depolarization and subsequent reduction in I_{Na} availability. The observation that this voltage-independent suppression of $(dV/dt)_{max}$ in ventricle is abolished in the presence of Ba^{2+},[16] suggests that it is due to the larger I_{Kl} in these cells. It appears likely that the observed differences in the $[K^+]_o$ dependence of θ in our simulations are also related to the size of I_{Kl}.

Separation of the Effects of Elevated $[K^+]_o$

In an attempt to separate the effects of reduced $V_{thresh}-V_{rest}$ and I_{Na} availability (which can be expected to be similar in atrial and ventricular cells) from those of $R_{in}(I_{Kl})$, we designed the following simulation paradigm: (1) reduced $V_{thresh}-V_{rest}$ was simulated without changes in R_{in} or I_{Kl} by shifting the voltage dependence of I_{Na} activation (m) in the hyperpolarizing direction (as opposed to shifting V_{rest} in the depolarizing direction with increased $[K^+]_o$); (2) reduced availability of I_{Na} at V_{rest} was simulated without changes in R_{in} or I_{Kl} by shifting the voltage dependence of I_{Na} inactivation (h) in the hyperpolarizing direction; and (3) reduced R_{in} was simulated without changing V_{rest} or I_{Na} availability by scaling and shifting I_{Kl} so that its value remains constant at V_{rest} although its slope changes [inset in Fig. 4(A)].

Simulations based on shifts in I_{Na} gating variables confirm that individual shifts in the activation (m) and inactivation (h) voltage dependence of I_{Na} [Figs. 3(A) and 3(B)] have the expected effects on θ. Increasing the depolarization needed to reach threshold by shifting m in the depolarizing direction suppresses θ, as does reducing the availability of I_{Na} at V_{rest} by shifting h in the hyperpolarizing direction. When m and h are simultaneously shifted by the same amount, hyperpolarizing shifts of 5–10 mV produce an increase in θ (supernormal conduc-

tion), whereas larger shifts reduce θ. Given that a 10 mV shift in the K^+ Nernst potential corresponds to an increase in $[K^+]_o$ from the nominal 5.4 to 8 mM, this is in close agreement with the peak of the $[K^+]_o$ dependence of θ [Fig. 3(C)]. Moreover, it supports the conclusion that the combined effects of reduced $V_{thresh}-V_{rest}$ (increasing excitability) and reduced I_{Na} availability (reducing excitability) underlies the biphasic $[K^+]_o$ dependence of θ as suggested by Shaw and Rudy.[12]

Simulations with varying R_{in} show that varying the slope of I_{Kl} around the nominal value in the human atrial model produces only minor changes in θ (decrease in θ for decrease in R_{in}). The conductance of I_{Kl} is approximately proportional to the square root of $[K^+]_o$, and thus a range of I_{Kl} slopes from 0.5 to 2 times nominal corresponds to a $[K^+]_o$ range of about 1–20 mM. Ventricular cells, on the other hand, have much smaller R_{in} than atrial cells and therefore operate around a completely different point on the curve in Fig. 4(A). The Luo–Rudy model, scaled to the size of the human atrial model, has an input resistance that is approximately one tenth of that in the human atrial model. As indicated in Fig. 4(A), a ventricular cell would therefore be expected to operate in a range where the dependence of θ on R_{in} is much steeper than it is for the atrial model. It is therefore likely that $[K^+]_o$-dependent changes in I_{Kl} slope can be an important factor in determining θ in ventricular cells. Obviously, this human atrial model with reduced R_{in} is not a valid model of ventricular electrophysiology; however, it can provide an interesting approximation that is applicable during the action potential upstroke. This is supported by the results of Shumaker *et al.*,[13] who found that a ''reduced'' model consisting of only I_{Kl} and I_{Na} can accurately reproduce the foot and upstroke of the action potential in a similar model of one-dimensional conduction.

The saturation of the effect of R_{in} on θ at high R_{in} can be understood in terms of the simple equivalent circuit in Fig. 4(B). As I_{Na} is activated in the leading cell (switch closes in cell 1), the membrane voltage of the following cell (cell 2) will exponentially approach an asymptotic value given by

$$v_{2,\infty}=\frac{E_{Na}R_{in}}{R_{in}+R_j+R_{Na}}+\frac{E_k(R_{Na}+R_j)}{R_{in}+R_j+R_{Na}}.$$

In essence, the circuit consists of two superimposed voltage dividers: A fraction of E_{Na} determined by the ratio of R_{in} to the sum of the three resistances is used to depolarize cell 2. This is opposed by a fraction of E_K determined by the ratio of the sum of R_{Na} and R_j to the sum of all three resistances. Note that if R_{in} is very large compared to R_{Na} and R_j, the first term in the equation above will be approximately equal to E_{Na}, whereas the second term will be close to zero. Thus, if $R_{in} \gg R_{Na}+R_j$, the coupling between the cells will be maximally efficient and the exact value of R_{in} of little importance. When R_{in} is comparable to R_{Na} and R_j, it becomes an important factor in determining the efficacy of coupling between the cells.

SUMMARY

The simulations presented in this article demonstrate that the $[K^+]_o$ dependence of θ in our model of conduction in a strand of human atrial cells has a biphasic shape. Slight increases in θ for moderate elevations of $[K^+]_o$ are due to a reduction in the distance from V_{rest} to the excitation threshold, $V_{thresh}-V_{rest}$. For larger elevations of $[K^+]_o$, however, the combined effects of reduced I_{Na} availability at V_{rest} and reduced R_{in} dominate and θ is gradually reduced until conduction fails around $[K^+]_o=17$ mM. Our results also demonstrate that the effects on θ of varying R_{in} around its nominal value for the human atrial model are relatively minor. However, if nominal R_{in} is reduced so that it becomes comparable to the sum of the gap junctional resistance and the membrane resistance when I_{Na} channels are open (as is the case in the ventricle), the sensitivity of θ to R_{in} is dramatically increased. Thus, our results suggest that conduction in the ventricle may be considerably more sensitive to $[K^+]_o$ than in the atrium or in other myocytes characterized by high input resistance, e.g., those from the sinoatrial or atrioventricular nodes or from Purkinje fibers.

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