Role of $I_{Kur}$ in Controlling Action Potential Shape and Contractility in the Human Atrium

Influence of Chronic Atrial Fibrillation

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Background—The ultrarapid outward current $I_{Kur}$ is a major repolarizing current in human atrium and a potential target for treating atrial arrhythmias. The effects of selective block of $I_{Kur}$ by low concentrations of 4-aminopyridine or the biphenyl derivative AVE 0118 were investigated on right atrial action potentials (APs) in trabeculae from patients in sinus rhythm (SR) or chronic atrial fibrillation (AF).

Methods and Results—AP duration at 90% repolarization (APD$_{90}$) was shorter in AF than in SR (300 ± 16 ms, n = 6, versus 414 ± 10 ms, n = 15), whereas APD$_{90}$ was longer (35 ± 9 ms in AF versus 5 ± 2 ms in SR, P < 0.05). 4-Aminopyridine (5 μmol/L) elevated the plateau to more positive potentials from $-21 ± 3$ to $-6 ± 3$ mV in SR and $0 ± 3$ to $+12 ± 3$ mV in AF. 4-Aminopyridine reversibly shortened APD$_{90}$ from 414 ± 10 to 350 ± 10 ms in SR but prolonged APD$_{90}$ from 300 ± 16 to 320 ± 13 ms in AF. Similar results were obtained with AVE 0118 (6 μmol/L). Computer simulations of $I_{Kur}$ block in human atrial APs predicted secondary increases in $I_{CaL}$ and in the outward rectifiers $I_K$ and $I_{Kur}$, with smaller changes in AF than SR. The indirect increase in $I_{CaL}$ was supported by a positive inotropic effect of 4-aminopyridine without direct effects on $I_{CaL}$ in atrial but not ventricular preparations. In accordance with the model predictions, block of $I_{Kur}$ with E-4031 converted APD shortening effects of $I_{Kur}$ block in SR into AP prolongation.

Conclusions—Whether inhibition of $I_{Kur}$ prolongs or shortens APD depends on the disease status of the atria and is determined by the level of electrical remodeling. (Circulation. 2004;110:2299-2306.)

Key Words: ion channels ▪ potassium channel blockers ▪ contraction ▪ action potentials ▪ fibrillation

The cardiac repolarization process is regulated by several outward currents, of which the ultrarapid delayed rectifier potassium current ($I_{Kur}$) is thought to play a major role. This current is absent in the ventricles and hence represents a suitable target for selectively modulating action potentials (APs) in the atria.1–3 The selective blocker of $I_{Kur}$, 4-aminopyridine in low micromolar concentrations is expected to prolong the AP duration (APD). However, experimental results in human atrial preparations from patients with sinus rhythm (SR) are inconsistent with shortening of APD in multicellular trabeculae4 and prolongation of APD in isolated atrial myocytes.1 Although block of $I_{Kur}$ and the subsequent prolongation of the APD are expected to be beneficial in chronic atrial fibrillation (AF), the experimental proof is still lacking. Furthermore, AF itself induces shortening of APD and effective refractory period, known as electrical remodeling, that is associated with changes in expression and activity of the involved ion channels.5 Human $I_{Kur}$ was found to be reduced by $\approx 50\%$, whereas other groups reported no changes.5

To predict the AP alterations associated with $I_{Kur}$ block during chronic AF, Courtemanche et al2 simulated these changes in a model of human APs in AF and demonstrated that the reduction of $I_{Kur}$ was associated with prolongation of APD. However, this article only predicted the changes without experimental verification.

Here, we studied the effects of $I_{Kur}$ block with 4-aminopyridine and with the new $I_{Kur}$ blocker, the biphenyl derivative AVE 0118, on APs in trabeculae from SR and AF patients. The impact of $I_{Kur}$ block on other atrial currents was predicted by simulating APs in a modified Luo-Rudy model, and the predictions were tested experimentally by recording APs or force of contraction ($F_c$) in trabeculae or by measuring membrane currents in isolated atrial myocytes.

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Human myocytes were isolated from atrial appendages as previously described.\(^6\) \(I_{Ca,L}\) and \(I_{K_a}\) were measured with conventional voltage-clamp technique as previously described.\(^6,7\) Mean cell capacitance was 101±6.5 pF (n=29).

**Measurement of \(F_c\)**

Pairs of right atrial or ventricular trabeculae were mounted in organ baths filled with 50 mL of buffer (composition in mmol/L: NaCl 126.7, KCl 1.8, MgCl\(_2\) 1.05, NaHCO\(_3\) 22.0, NaHPO\(_4\) 0.42, EDTA 0.04, and glucose 5.0, equilibrated with O\(_2\)/CO\(_2\) [95:5] at 37°C, pH 7.4).\(^8\) The bath solution contained 200 nmol/L (−)-propranolol to exclude effects mediated through β-adrenoceptors. The preparations were paced (0.5 Hz, 5-ms stimulus, 10% above threshold intensity) and were stretched to 80% of the length associated with maximum developed force. After an equilibration period of 30 minutes, the effects of 4-aminopyridine or AVE 0118 on \(F_c\) were determined by cumulatively increasing concentrations every 20 minutes.

**Action Potential Simulations**

For simulating the shapes of human atrial APs, we modified mathematical models described in the literature.\(^9–11\) The incorporated membrane currents and transporters and factors controlling intracellular ion concentrations are listed in the Appendix (see online-only Data Supplement), which also contains specific kinetic parameters, constants of ion currents, and the equations used for current calculations. Maximum current conductances of \(I_{Ca,L}\), \(I_{Na,K}\), \(I_{K_a}\), and \(I_{Na,K}\) were adapted to simulate the characteristic AP shapes. For AP simulation in chronic AF, original current data were taken from the literature and, when not available, amplitudes were extrapolated from changes in channel expression.

As an approximation, APs were assumed to be spatially uniform, i.e., conduction within the preparation was neglected. Changes of membrane potential were calculated for space-clamp conditions as follows: d(V\(_{m}\))/dt = \(-\sum I(V_{m})/C_{m}\), with \(I(V_{m}) = I_{Ca,L} + I_{Na,K} + I_{K_a} + I_{K_Ca} + I_{K,Ch} + I_{Na,K} + I_{Ca,T} + I_{K_{par}} + I_{Na,K} + I_{Na,K}\) and \(I_{m}\) = stimulus current of \(-90\) μA/cm\(^2\) applied 0.5 ms at beginning of each cycle, and \(C_{m}\) = membrane capacitance (specific C\(_m\) assumed to be 1 μF/cm\(^2\)).

Numerical integration of d(V\(_{m}\))/dt was performed according to a modified Euler method suggested by Rush and Larsen.\(^12\) The length of the time steps was varied between 0.02 and 20 ms, depending on the extent of resultant voltage changes. Momentary values of gating variables were calculated from analytical solution of the related first-order differential equations: \(x_{\tau} = x_{0}(V_{m}) - x_{0}(V_{m}) \times \exp[-dt/\tau(V_{m})]\), with \(x_0\) = ith timestep (ie, \(t = t_{i} + \Delta t\)) and \(x_{0}(V_{m}) = \) voltage-dependent steady-state value, \(\tau(V_{m}) = \) voltage-dependent time constant.

Simulated APs, currents, and ion concentrations were allowed to stabilize for at least 200 cycles. The model was implemented in Turbo Pascal 6.0. For further details of the model, see Appendix.

**Statistical Analysis**

Differences between continuous data were compared by unpaired Student t test or 1-way ANOVA. Frequency data were analyzed with \(\chi^2\) statistics. Data are mean±SEM. A value of \(P<0.05\) was considered statistically significant.

## Results

**Effect of 4-Aminopyridine on AP Configuration in SR and AF**

Resting membrane potentials were −75±1 mV in SR (n=15) and significantly more negative in AF (−80±3 mV, n=6, \(P<0.05\)). In accordance with our previous results,\(^14\) APD at 20% of repolarization (APD\(_{20}\)) was shorter in SR (5±2 ms) than in AF (35±9 ms, \(P<0.05\)), whereas APD\(_{50}\) was longer in SR (414±10 ms) compared with AF (300±16 ms, \(P<0.05\)).

| TABLE 1. Characteristics of Patients in SR and Chronic AF |
|-----------------------------|-----------------------------|
| **SR** | **AF** |
| No. | 34 | 18 |
| Sex, M/F | 25/9 | 11/7 |
| Age, y | 68±2 | 64±4 |
| BMI, kg/m\(^2\) | 29±1 | 26±1\(^*\) |
| CAD, n | 26 | 3\(^*\) |
| AVE/MVD, n | 5 | 10\(^*\) |
| CAD+AVE/MVD, n | 3 | 5 |
| Hypertension, n | 28 | 13 |
| Pulmonary hypertension, n | 3 | 10\(^*\) |
| Diabetes, n | 14 | 8 |
| Hyperlipidemia, n | 15 | 9 |
| LVEF, % | 61±3 | 58±3 |
| LVEDP, mm Hg | 14±1 | 14±2 |
| LA, mm | 38±2 | 51±4\(^*\) |
| LVEDD, mm | 51±3 | 57±3 |
| Cardiovascular medication, n |
| Digitalis | 4 | 6\(^*\) |
| ACE inhibitors/AT, blockers | 23 | 10 |
| β-Blockers | 31 | 9\(^*\) |
| Calcium channel blockers | 2 | 1 |
| Diuretics | 14 | 13\(^*\) |
| Nitrates | 17 | 7 |
| Lipid-lowering drugs | 19 | 3\(^*\) |

\(\text{CAD indicates coronary artery disease; AVE, aortic valve disease; MVD, mitral valve disease; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVEDP, left ventricular end-diastolic pressure; LA, left atrial diameter; and AT, angiotensin receptor.} \)

\(^*P<0.05\) values from nonpaired Student t test for continuous variables and from \(\chi^2\) test for categorical variables.
In the presence of 4-aminopyridine (5 μmol/L), the potentials of the notch and dome (SR) and of the plateau shoulder (AF) were shifted to more positive values, leading to a significant increase in APD$_{20}$ from 5100 ± 20 to 1250 ± 5 ms in SR ($P < 0.05$) and from 35 ± 9 to 78 ± 5 ms in AF ($P = 0.002$, Figure 1, A and B). The final repolarization phase was accelerated in both groups; however, APD$_{90}$ was shortened from 414 ± 10 to 350 ± 10 ms in SR ($P < 0.0001$) but was prolonged from 300 ± 16 to 320 ± 13 ms in AF ($P < 0.006$; Figure 1, C and D), suggesting that the directions of APD$_{90}$ changes are different in SR and AF. The effects of 4-aminopyridine were reversible on washout.

In SR preparations, the mean notch potential, ie, the minimum potential after the initial rapid repolarization phase, was shifted by 4-aminopyridine (5 μmol/L) from −32 ± 4 to −22 ± 5 mV ($P < 0.003$), and the mean dome potential, ie, the most positive plateau potential before final repolarization, was shifted from −28 ± 4 to −13 ± 6 mV ($P < 0.001$). Because APs in AF did not exhibit the typical notch as in SR, we introduced the parameter “plateau potential” for analysis of changes in this potential range. Plateau potential is defined as the mean amplitude within the time window of 20 to 80 ms after the upstroke of the AP (Figure 1, A and B). In SR, the plateau potential was shifted by 4-aminopyridine (5 μmol/L) from −21 ± 3 to −6 ± 3 mV ($P < 0.0001$, Figure 1E). In AF, the plateau potential was more positive (0 ± 3 mV, $P = 0.0001$ versus SR) and was shifted by 4-aminopyridine to +12 ± 3 mV ($P = 0.0012$, Figure 1F).

The effect of 4-aminopyridine on the shift in notch-and-dome potentials was concentration-dependent (0.3 to 100 μmol/L, Figure 2, A and B). In SR, the notch potential became less negative and shifted from −23 ± 2 to −4 ± 2 mV with 100 μmol/L 4-aminopyridine (Figure 2, A and C, n = 5, $P < 0.001$), and the respective dome potential was changed from −18 ± 1 to 0 ± 2 mV ($P < 0.001$). Nonlinear curve fitting resulted in EC$_{50}$ values of 15 μmol/L 4-aminopyridine for elevation of notch potential and 14 μmol/L for elevation of dome potential (Figure 2C). In AF, the effect of 4-aminopyridine on the plateau potential was also concentration-dependent, with an EC$_{50}$ value of 28 μmol/L in 1 experiment (Figure 2, B and D).

Model Simulations of APs in SR and AF: Block of $I_{K_{ur}}$

Inserting experimentally estimated parameters into the mathematical model of human atrial APs (see Appendix) provided the spike-and-dome shape typical for tissue from SR patients (compare Figures 1A and 3). Selective inhibition of $I_{K_{ur}}$ by 4-aminopyridine was simulated by setting the current to 20%
of its regular value in SR (see Table 2). The model reproduced the observed shifts of notch-and-dome potentials to more positive values (Figure 3) and shortened APD90. Block of \( I_{Kur} \) induced a series of indirect effects on other currents because of their voltage and time dependence during the course of a free-running action potential. The model predicted peak \( I_{Ca,L} \) to increase by 37% at the elevated plateau potential (Figure 3) and increases in the outward potassium currents \( I_{Ks} \) and \( I_{Kur} \) by 80% and 50%, respectively.

The characteristic triangular shape of APs in AF was reproduced by setting conductances of \( I_{Ks}, \ I_{Ca,L}, \ I_{Kur}, \ \) and \( I_{Kur} \) to values of reported ion current densities or channel expression (Figures 1B and 3; see Reference 5 and Table 2). The effect of 4-aminopyridine was simulated by setting the expression (Figures 1B and 3; see Reference 5 and Table 2). The effect of 4-aminopyridine on \( Fc \) was a result of the blockade of \( I_{Ca,L} \) and \( I_{Kur} \), which are not measured.15 Indeed, 4-aminopyridine (0.3 \( \mu \)mol/L to 1 \( \mu \)mol/L) did not affect \( Fc \) in ventricular trabeculae (Figure 4, C and D), excluding a direct effect of 4-aminopyridine on Ca\(^{2+}\) release or contractile machinery.

According to the model prediction in SR, the shortening of APD90 by block of \( I_{Kur} \) is expected to be induced by an increase in \( I_{Ks} \). Block of \( I_{Ks} \) with E-4031 (1 \( \mu \)mol/L) prolonged APD90, although the effect did not reach the level of statistical significance (\( P=0.366 \), n=5, Figure 5, A and C). In the presence of E-4031, 4-aminopyridine (25 \( \mu \)mol/L) no longer shortened but rather prolonged APD90 from 412±43 to 483±33 ms (n=5, \( P=0.2217 \); versus control, \( P=0.0249 \)) and significantly elevated the notch and dome potentials from −30±2 to −19±3 mV (n=5, \( P<0.05 \)) and from −27±2 to −14±3 mV (n=5, \( P<0.001 \)), respectively. These effects were reproduced in the model simulation by reducing the conductance of \( I_{Ks} \) by 95% and that of \( I_{Kur} \) by 90% (Figure 5B).

**Effect of the \( I_{Kur} \) Blocker AVE 0118 on AP in SR and AF**

The effects of \( I_{Kur} \) inhibition were verified with the new \( I_{Kur} \) blocker AVE 0118 (6 \( \mu \)mol/L). AVE 0118 revealed the typical changes in AP shape as found with low concentrations of 4-aminopyridine (5 \( \mu \)mol/L), i.e., elevation of the plateau potential from −16.3±2.4 to −6.7±2.4 mV (n=9, \( P<0.01 \)) in the presence of 6 \( \mu \)mol/L AVE 0118, and shortening of APD90 from 343±14 to 328±17 ms (\( P=0.066 \)) in SR. In AF, the plateau amplitude increased from −24±3.6 to 8.8±3.6 mV (n=6, \( P<0.001 \)) and APD90 increased from 260±14 to 280±13 ms (\( P<0.05 \); Figure 6).
Discussion

The concept of block of $I_{Kur}$ as a therapeutic target in AF is widely accepted, despite inconsistent experimental and theoretical evidence for changes in APD. Here, we report that selective block of $I_{Kur}$ shortens APD of human atrial trabeculae from SR but prolongs APD in AF. Changes in APD in SR and AF were consistent with secondary current changes as predicted by a modified Luo-Rudy model and were verified experimentally.

Effects of Block of $I_{Kur}$ on Shapes of Atrial APs in SR and AF

In low concentrations, 4-aminopyridine is a selective blocker of $I_{Kur}$. In earlier work, we found that 4-aminopyridine blocks $I_{Kur}$ and $I_{to,f}$ in human atrial myocytes with IC$_{50}$ values of 8 $\mu$mol/L and 1 mmol/L, respectively. Similar values were published by others (ie, 49 $\mu$mol/L for $I_{Kur}$ and 1.9 mmol/L for $I_{to,f}$).

Block of repolarizing outward current is expected to prolong APD; however, we observed shortening in SR preparations instead. In the literature, shortening, prolongation, and even no effect at all have been reported. How can these inconsistencies be reconciled? The shape of the cardiac AP is the result of the balanced activity of several ion currents. Provided that 4-aminopyridine at the concentrations used is in fact selective for $I_{Kur}$ block, APD shortening in SR must be associated with alterations in additional currents. In this context, the pronounced elevation of the action potential plateau may provide an important clue because enhanced amplitude of $I_{Ca,L}$ at more positive potentials could activate repolarizing outward currents that would shorten APD.

In AF, block of $I_{Kur}$ resulted in the expected APD prolongation. The characteristic triangular AP shape in AF compared with the spike-and-dome configuration in SR is a result of electrical remodeling that comprises changes in several ion currents.
conductances. The densities of \( I_{\text{Ca,L}} \) and \( I_{\text{to,f}} \) are reduced by \( \approx 70\% \), \( 16,17 \) and \( \approx 60\% \), \( 16,18,19 \) respectively, and inward rectifier \( I_{\text{Kr}} \) is increased by \( \approx 100\% \). \( 14,16,18,20 \) From these considerations, it follows that selective block of \( I_{\text{Kur}} \) (or any other current) will perturb the balance of ion channel activation differently in AF and SR and may result in different patterns of secondary effects.

Computer Simulations: Indirect Effects of 4-Aminopyridine on \( I_{\text{Ca,L}} \)

To predict individual current changes secondary to selective block of \( I_{\text{Kur}} \), we used a computer model of AP simulation. For this purpose, ion conductances in the Luo-Rudy model \( 9 \) were set to the experimentally observed values reported

Figure 4. Effect of 4-aminopyridine on \( F_c \) in isolated human atrial and ventricular preparations. A, Original recordings of \( F_c \) with increasing concentrations of 4-aminopyridine (300 nmol/L to 1 mmol/L) for atrial trabeculae from an SR patient (top) and an AF patient (below). B, Concentration-dependent effects of 4-aminopyridine on \( F_c \) in atrial preparations from SR (open squares) and AF (open circles) patients (EC\(_{50}\)=52 \( \mu \)mol/L, SR, and EC\(_{50}\)=36 \( \mu \)mol/L, AF). Maximum contractile responses were tested with high extracellular Ca\(^{2+}\) (8 mmol/L) at end of each experiment. C, Original registrations of \( F_c \) in time-matched controls (TMC, top) and with 4-aminopyridine (0.3 \( \mu \)mol/L to 1 mmol/L) of human ventricular trabeculae (below). D, Concentration-dependent effects of 4-aminopyridine on \( F_c \) in human ventricular preparations.

Figure 5. Effect of block of \( I_{\text{Kur}} \) by 4-aminopyridine in presence of \( I_{\text{Kr}} \) block with E-4031. A, Original AP registration in SR; C, control AP (solid line), 20 minutes after E-4031 (1 \( \mu \)mol/L, short dashes), and 20 minutes after 4-aminopyridine (25 \( \mu \)mol/L) in presence of E-4031 (long dashes). B, Simulated AP; C, control, after reducing \( g_{\text{max}} \) of \( I_{\text{Kr}} \) to 5\% (dashed line) and \( g_{\text{max}} \) of \( I_{\text{Kur}} \) to 10\% of control value. C, Means of APD\(_{90}\) (left), notch potential (middle), and plateau potential (right) for atrial trabeculae from SR patients (n=5, *P<0.05).
recently for human AF. The model simulated the characteristic AP shapes. For selective block of $I_{Kur}$ in SR APs, the model produced a more pronounced spike-and-dome configuration. The shift of the plateau to more positive potentials was associated with enhanced $I_{Cal}$ activation in the model (although 4-aminopyridine had no direct effects on $I_{Cal}$) and is expected to increase systolic Ca$^{2+}$ influx during a free-running AP. Indeed, 4-aminopyridine significantly increased $I_{Kr}$ in atrial trabeculae in a concentration-dependent manner (see Figure 4) in SR and AF, respectively. Although the positive inotropic effect was much smaller in AF, it is considered to be clinically interesting, because atrial contractility is already impaired in AF and all other drugs currently used in the treatment of AF, eg, β-adrenergic blockers or calcium channel blockers, have a negative inotropic effect.

**Computer Simulations: Indirect Effects of 4-Aminopyridine on $I_{Kr}$**

Secondary enhancement of outward currents as an explanation for APD shortening in SR by block of $I_{Kur}$ was also predicted by the model. As the likely candidates, the model identified $I_{Kr}$ and $I_{Ks}$. Because of its slow activation kinetics, $I_{Kr}$ will not play a major role in the course of the short atrial APs. Conversely, the impact of $I_{Ks}$ was examined experimentally; pharmacological block of $I_{Ks}$ in trabeculae from SR unMASKS THE APD-prolonging effect of $I_{Kr}$ block (see Figure 5). Therefore, we speculate that 4-aminopyridine prolongs APD in atrial myocytes, because $I_{Ks}$ may be absent because of the enzymatic isolation procedure, as was shown for canine atrial myocytes.

The model simulation of the human atrial SR AP reproduces the experimentally observed APD shortening that is induced by $I_{Kur}$ block. However, this experimental finding is reproduced only when $I_{Ks}$ is set to sufficiently high values (Table 2). If low values are used (see, for instance, Nygren et al23), $I_{Kur}$ block is not proved with current measurements, the APD-prolonging effect of $I_{Kr}$ block by E-4031 (Figure 5) points to a prominent role of this current in atrial repolarization, supported also by current measurements of $I_{Ks}$ in human atrium.24 In the presence of $I_{Ks}$ block, $I_{Kur}$ inhibition further prolonged APD. We therefore assume that in multicellular trabeculae, $I_{Ks}$ was fully available for repolarization. In conscious dogs, the $I_{Ks}$ blocker ibutilide prolonged atrial monophasic APs and effective refractory period,25 providing evidence for a prominent $I_{Ks}$ contribution. Because $I_{Cal}$ is reduced in AF, block of $I_{Kur}$ cannot produce much indirect increase in $I_{Cal}$, and therefore the plateau is only slightly elevated. Because of enhanced $I_{Kr}$ in AF, rapid and strong induction of the repolarization process abbreviates the time window for activation of $I_{Ks}$ and thus reduces its repolarizing potency. All interacting factors together will produce an AP-prolonging effect of $I_{Kur}$ block, which possibly represents the antirhythmic potency of putative $I_{Kur}$ blockers.

**Study Limitations**

The majority of patients donating tissue samples suffered from coronary artery disease. Therefore, AP measurements from SR trabeculae may not be considered to be fully representative of APs from trabeculae of a healthy population. In addition, the patients’ medications may have additional effects. The large variability in action potential shapes may represent this inhomogeneity of the material.

Early repolarization is controlled not only by $I_{Kur}$ but also by $I_{Ks}$. Although low concentrations of 4-aminopyridine are selective for block of $I_{Kur}$, a contribution of $I_{Ks}$ block cannot be excluded at larger concentrations. In the absence of selective blockers for $I_{Kur}$, model simulations are useful for estimating the consequences of $I_{Ks}$ block on atrial AP. Like $I_{Kur}$ block, reduced basal conductance of $I_{Kur}$ shifted the notch potential to more positive values and abbreviated APD$_{50}$ in

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**TABLE 2. Maximum Conductances, $g_{max}$, of the Main Currents Incorporated in the Mathematical Model for Action Potential Simulation**

<table>
<thead>
<tr>
<th>Current</th>
<th>SR</th>
<th>AF</th>
<th>Percent Change From SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Cal}$</td>
<td>$7.2 \times 10^{-2}$</td>
<td>$2.3 \times 10^{-2}$</td>
<td>-68%</td>
</tr>
<tr>
<td>$I_{Ks}$</td>
<td>$1.8 \times 10^{-2}$</td>
<td>$8.64 \times 10^{-3}$</td>
<td>-52%</td>
</tr>
<tr>
<td>$I_{Kt}$</td>
<td>$1.6 \times 10^{-1}$</td>
<td>$6.24 \times 10^{-2}$</td>
<td>-61%</td>
</tr>
<tr>
<td>$I_{Kd}$</td>
<td>$6.0 \times 10^{-2}$</td>
<td>$6.0 \times 10^{-2}$</td>
<td>Unchanged</td>
</tr>
<tr>
<td>$I_{Kt}$</td>
<td>$5.0 \times 10^{-2}$</td>
<td>$5.0 \times 10^{-2}$</td>
<td>Unchanged</td>
</tr>
<tr>
<td>$I_{Kt}$</td>
<td>$4.9 \times 10^{-2}$</td>
<td>$9.6 \times 10^{-2}$</td>
<td>+98%</td>
</tr>
<tr>
<td>$I_{Kur}$</td>
<td>$1.5 \mu A/\mu F$</td>
<td>$2.5 \mu A/\mu F$</td>
<td>+67%</td>
</tr>
</tbody>
</table>

Values are in mS/$\mu F$ except as noted. For simulations of AF action potentials, channel conductances were adapted to correspond to the reported changes in current density or were extrapolated from changes in mRNA and protein levels.
SR and only slightly prolonged APD\(_{\text{m}}\) in AF. In contrast to \(I_{\text{Kur}}\) block, selective block of \(I_{\text{Kr}}\) did not elevate the dome potential or enhance the spike-and-dome configuration (data not shown). The rapid \(I_{\text{Kr}}\) inactivation most likely limits indirect enhancement of \(I_{\text{K}}\) if \(I_{\text{Kr}}\) is blocked.

**Conclusions**

We hypothesize that \(I_{\text{Kur}}\) is a major determinant in controlling action potential shape and therefore also contractility in the human atrium. The antiarrhythmic potency of \(I_{\text{Kur}}\) inhibitors is determined largely by the level of electrical remodeling of the diseased atrium. Although the antiarrhythmic effectiveness of \(I_{\text{K}}\) blockers is significantly attenuated in chronic AF, \(26\) selective \(I_{\text{K}}\) blockers may be more potent in prolonging atrial refractory period in chronic AF than in SR and may therefore be more efficient in terminating AF than in maintaining SR.

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