Short-Term Effects of Rapid Pacing on mRNA Level of Voltage-Dependent K⁺ Channels in Rat Atrium

Electrical Remodeling in Paroxysmal Atrial Tachycardia

Takeshi Yamashita, MD; Yuji Murakawa, MD; Noriyuki Hayami, MD; Ei-ichi Fukui, MD; Yuji Kasaoka, MD; Masashi Inoue, MD; Masao Omata, MD

Background—Atrial fibrillation causes electrophysiological changes of the atrium, thereby facilitating its maintenance. Although the expression of ion channels is modulated in chronic atrial fibrillation, it is yet unknown whether paroxysmal atrial fibrillation can also lead to electrical remodeling by affecting gene expression.

Methods and Results—To examine the short-term effects of rapid pacing on the mRNA level of voltage-dependent K⁺ channels, high-rate atrial pacing was performed in Sprague-Dawley rat hearts. Total RNA was prepared from the atrial appendages from 0 to 8 hours after the onset of pacing, and mRNA levels of Kv1.2, Kv1.4, Kv1.5, Kv2.1, Kv4.2, Kv4.3, erg, KVLQT1, and minK were determined by RNase protection assay. Among these 9 genes, the mRNA level of the Kv1.5 channel immediately and transiently increased, with bimodal peaks at 0.5 and 2 hours after the onset of pacing. Conversely, the pacing gradually and progressively decreased the mRNA levels of the Kv4.2 and Kv4.3 channels. The increase of Kv1.5 and the decrease of Kv4.2 and Kv4.3 mRNA levels were both rate dependent. In correspondence with the changes in the mRNA level, Kv1.5 channel protein transiently increased in the membrane fraction of the atrium during a 2- to 8-hour pacing period. Electrophysiological findings that the shortening of the action potential produced by 4-hour pacing was almost abolished by a low concentration of 4-aminopyridine implied that the increased Kv1.5 protein was functioning.

Conclusions—Even short-term high-rate atrial excitation could differentially alter the mRNA levels of Kv1.5, Kv4.2, and Kv4.3 in a rate-dependent manner. In particular, increased Kv1.5 gene expression, having a transient nature, implied the possible biochemical electrical remodeling unique to paroxysmal tachycardia. (Circulation. 2000;101:2007-2014.)

Key Words: arrhythmia • fibrillation • electrophysiology • RNA

The progressive feature of atrial fibrillation (AF) has been attributed to the alteration of electrophysiological properties of the atrial myocardium,1 ie, “atrial remodeling by AF.” Clarification of the mechanisms underlying the AF-induced electrical remodeling is presumed to be the key to effective treatment.1,2 In humans, even AF of several minutes (=10 minutes) shortens atrial refractoriness.3 This shortening is considered to result from physiological responses to the intracellular Ca²⁺ overload by high-rate atrial excitation, because this shortening recovered rapidly within several minutes after cessation of AF.4 In contrast, long-lasting AF shortens the atrial refractoriness in a different manner. Patch-clamp studies of the atrial myocyte from experimental models or of human chronic AF revealed that AF reduces the expression levels of some ion channels, including the L-type Ca²⁺ channel, transient outward current (Iₒ), and Na⁺ channel.5–7 Therefore, both physiological responses and biochemical reconstruction may underlie the electrical remodeling by paroxysmal and chronic AF, respectively.

In addition to these mechanisms, however, before considering a prophylactic therapy of several-hour paroxysmal AF, it is important to know whether it causes only physiological responses or whether it also induces electrophysiological changes due to alterations of channel gene expression (biochemically based remodeling). Changes in vulnerability to AF took hours to recover in a 24-hour rapid-pacing model, suggesting that electrophysiological changes occur in paroxysmal AF.8 In the present study, we tested the hypothesis that the mRNA levels of voltage-dependent K⁺ channel genes are altered by several-hour high-rate atrial excitation and that this alteration possibly leads to electrical remodeling in paroxysmal AF.9

Methods

Preparation of Tachycardia Models
Sprague-Dawley rats aged 12 weeks were used in the present study. Rats were anesthetized with pentobarbital (50 mg/kg) and ventilated with a volume-cycled respirator. A quadripolar electrode catheter...
Preparation of DNA Templates

DNA templates of 9 voltage-dependent K⁺ channels known to be expressed in rat hearts (Kv1.2, Kv1.4, Kv1.5, Kv2.1, Kv4.2, Kv4.3, erg, KvLQT1, and minK)10 were prepared by reverse transcription–polymerase chain reaction (RT-PCR, 30 cycles at 94°C for 30 seconds, at 65°C for 30 seconds, and at 72°C for 90 seconds, with the Access RT-PCR system, Promega) from total RNA isolated from the rat atria. The amplified cDNA fragments were subcloned into PCR II vectors (Invitrogen) and confirmed by sequencing. The primers specific for each channel based on the known sequence are shown in Table 1. These plasmids were used to synthesize the antisense digoxigenin-labeled RNA probes.

RNA Preparation and RNase Protection Assay

Right and left atrial appendages were excised and quickly frozen in liquid nitrogen. Total RNA was extracted by using the acid guani- dinium isothiocyanate method.11 The mRNA levels of the voltage-dependent K⁺ channels were assayed by using RNase protection assay with an RPA II kit (Ambion). Amounts of 5 to 10 μg RNA were used for hybridization, RNase digestion, and recovery of protected RNAs and were transferred to a nylon membrane after being run on a denaturing gel. The membranes were incubated with anti-digoxigenin antibody conjugated to alkaline phosphatase; subsequently, the protected fragments were detected by using CSPD (Tropix). Chemiluminescent signals were quantified by a Lumino-Image Analyzer (LAS-1000, Fujifilm). The cyclophilin signals were used as internal controls.

Western Blot Analysis

Membrane fractions of the atrial myocardium were prepared according to the protocol described by Barry et al.12 Membrane proteins (30 µg) were fractionated by SDS-PAGE and transferred to polyvinylidi- dine difluoride membranes (Boehringer-Mannheim, GmbH). The membrane was incubated with polyclonal anti-Kv1.5, anti-Kv2.1, anti-Kv4.2, and anti-Kv4.3 obtained from rabbits (Upstate Biotech- nology and Chemicon International) and subsequently with goat anti-rabbit IgG conjugated to alkaline phosphatase (Boehringer-Mannheim).

Electrophysiological Study

To examine the functional aspects of the modified gene expression, monophasic action potentials (MAPs) were recorded in the isolated perfused hearts. After 4-hour rapid pacing (see Results), the hearts were rapidly excised and retrogradely perfused with Tyrode’s solution containing (mmol/L) NaCl 136.5, KCl 5.4, HEPES 5.5, CaCl₂ 1.8, and MgCl₂ 0.53 (pH 7.4). After 30 minutes of recovery maintained at sinus rhythm, MAPs were recorded from the right atrial appendage by using a conventional suction electrode at a constant pacing cycle length of 250 milliseconds.

Statistical Analysis

To examine the time course of the mRNA level of the voltage-dependent K⁺ channel genes, the value at the 0-hour time point after the rapid pacing was arbitrarily set to 1 U for quantitative comparisons. The mean values at different times after rapid pacing were compared with an ANOVA, and multiple comparisons were made by the Bonferroni modified t test. The mean values of the MAP duration were compared by unpaired t test. Statistical significance was set at P<0.05.

Results

Rapid Atrial Pacing Model of the Rat

Figure 1 shows ECG lead II, the atrial electrogram, and right atrial pressure (RAP) obtained in the rapid atrial pacing model of the rat. The ventricular rate and right atrial pressure significantly increased with rapid atrial pacing at a rate of 1200 bpm (from 382±5 to 462±58 bpm and from 3±1 to 9±2 mm Hg, respectively; both P<0.01). Values at different pacing rates are shown in Table 2.

No Effects of Rapid Pacing on the mRNA Level of 6 Voltage-Dependent K⁺ Channels

In all the atrial samples, the investigated voltage-dependent K⁺ channel genes (Kv1.2, Kv1.4, Kv1.5, Kv2.1, Kv4.2, Kv4.3, erg, KvLQT1, and minK) were expressed at appreciable mRNA levels, as reported previously.10 Among these 9

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**TABLE 1. PCR Primers Used for Amplification of Voltage-Dependent K⁺ Channel Genes**

<table>
<thead>
<tr>
<th>Channel</th>
<th>Sense</th>
<th>Antisense</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kv1.2 (267 bp)</td>
<td>5'-GACAAGTGTCCAAAGATCC</td>
<td>5'-GTTGGACTGAGTACATTAA</td>
</tr>
<tr>
<td>Kv1.4 (249 bp)</td>
<td>5'-GAGCTCCTACTTCTTTTCCT</td>
<td>5'-TATCTCTATTTGTCATACG</td>
</tr>
<tr>
<td>Kv1.5 (229 bp)</td>
<td>5'-CGAGATTTAAAGCCACCCTGG</td>
<td>5'-GATTATCTTCTGCATTG6GT</td>
</tr>
<tr>
<td>Kv2.1 (364 bp)</td>
<td>5'-GCTCTGTTTCTTCTGTCAGGAG</td>
<td>5'-CAGGCTAGAGACGCAACAGAC</td>
</tr>
<tr>
<td>Kv4.2 (308 bp)</td>
<td>5'-CTTCACATTCGCGCGCAT</td>
<td>5'-GTTGCCACCACTTGC6G</td>
</tr>
<tr>
<td>Kv4.3 (304 bp)</td>
<td>5'-GCTTGGGCTTTGTGACTCC</td>
<td>5'-CTGCGCTGCTGCATCAGT</td>
</tr>
<tr>
<td>KvLQT1 (300 bp)</td>
<td>5'-CTGCGCTGCTGCATCAGT</td>
<td>5'-AAGGAAGCGGATACCCGT</td>
</tr>
<tr>
<td>minK (541 bp)</td>
<td>5'-CGCCATCCCCGCTATCGGAG</td>
<td>5'-CTCACAGGGCTCTTCACACCG</td>
</tr>
<tr>
<td>erg (435 bp)</td>
<td>5'-TACACAGGGCTCTTCACACCG</td>
<td>5'-GAGCCAATGTGCAATGAGCGC</td>
</tr>
<tr>
<td>K1 (435 bp)</td>
<td>5'-CTCACAGGGCTCTTCACACCG</td>
<td>5'-GTTTCCACCACTTGC6G</td>
</tr>
<tr>
<td>K2 (435 bp)</td>
<td>5'-GAGCCAATGTGCAATGAGCGC</td>
<td>5'-CTCACAGGGCTCTTCACACCG</td>
</tr>
<tr>
<td>K3 (435 bp)</td>
<td>5'-GTTTCCACCACTTGC6G</td>
<td>5'-GAGCCAATGTGCAATGAGCGC</td>
</tr>
</tbody>
</table>

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**Figure 1.** Rapid pacing model of rat. Right atrial rapid pacing was performed through the electrode catheter introduced from cervical vein. ECG lead II, atrial electrogram (RA), and right atrial pressure (RAP) are shown.
channels, short-term (≤8-hour) rapid atrial pacing at a rate of 1200 bpm did not significantly alter the mRNA levels of Kv1.2, Kv1.4, Kv2.1, erg, KvLQT1, and minK (Figure 2; percent change at 8 hours: Kv1.2 12±6%, Kv1.4 2±16%, Kv2.1 9±10%, erg 8±4%, KvLQT1 5±10%, and minK 2±8±10%).

Effects of Rapid Pacing on Kv1.5, Kv4.2, and Kv4.3 mRNA Levels

In contrast to the 6 K⁺ channels that remained stable during the procedure, short-term rapid atrial pacing at a rate of 1200 bpm significantly altered the mRNA levels of 3 K⁺ channel genes (Kv1.5, Kv4.2, and Kv4.3), with differential alterations in the time course and direction among these K⁺ channels. A representative example is shown in Figure 3. The Kv1.5 mRNA level exhibited the most striking changes. With rapid atrial pacing, it immediately increased significantly, even at 0.5 hour after the onset of rapid pacing. The increase was maintained for 1 hour and then became more remarkable at 2 hours after the onset of pacing. Thereafter, the Kv1.5 mRNA level began to decrease and returned to the baseline value at 8 hours. Therefore, the Kv1.5 mRNA level showed a characteristic change of an immediate and transient nature. In contrast, mRNA levels in the other 2 K⁺ channels (Kv4.2 and Kv4.3) decreased significantly with rapid pacing over a more prolonged time course. The decrease in the mRNA level of Kv4.2 became significant at 2 hours after the onset of rapid pacing, whereas the mRNA level of Kv4.3 was slower and became significant at 4 hours. In addition, these changes in the 2 K⁺ channel mRNA levels were both progressive, not transient, during the 8-hour pacing. The mRNA levels of these 3 K⁺ channels in sham-operated animals did not change significantly within 8 hours after the operation.

Rate-Dependent Effects and Regional Inhomogeneities

To determine whether the changes in the mRNA levels of Kv1.5, Kv4.2, and Kv4.3 are not nonspecific effects, the effects of the pacing rate on these mRNA levels were determined. The mRNA levels of Kv1.5 at 0.5- and 2-hour pacing, Kv4.2 at 4-hour pacing, and Kv4.3 at 8-hour pacing were determined at various pacing rates, including sinus rhythm and 450, 600, 800, 1200, and 1500 bpm. As shown in Figure 4, all of these changes in the mRNA levels were definitely pacing-rate dependent, although the effects seemed

### Table 2. Ventricular Rate and Right Atrial Pressure in Rapid Pacing Model

<table>
<thead>
<tr>
<th>Pacing Rate, bpm</th>
<th>Ventricular Rate, bpm</th>
<th>Mean Right Atrial Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus</td>
<td>382±25</td>
<td>3±1</td>
</tr>
<tr>
<td>600</td>
<td>600±0*</td>
<td>4±2</td>
</tr>
<tr>
<td>800</td>
<td>682±28*</td>
<td>7±2*</td>
</tr>
<tr>
<td>1200</td>
<td>462±58*</td>
<td>9±2*</td>
</tr>
<tr>
<td>1500</td>
<td>422±68</td>
<td>9±3*</td>
</tr>
</tbody>
</table>

Values are mean±SEM (n=10 at each pacing rate).

*P<0.01 vs sinus.

Figure 2. Effects of rapid atrial pacing at 1200 bpm on mRNA levels of Kv1.2, Kv1.4, Kv2.1, rat-erg, KvLQT1, and minK. mRNA levels were determined by RNase protection assay with internal control of cyclophilin. In each panel, from left to right, samples from atria at baseline and at 0.5, 1, 2, 4, and 8 hours after onset of rapid pacing and samples from sham-operated animals at 8 hours after operation (C8) are shown. N represents the negative control with yeast tRNA. Lines and circles represent protected fragments of the channel gene and cyclophilin, respectively. Rapid pacing did not affect mRNA levels of these 6 channel genes (n=5).
to be almost saturated at a rate ≥1200 bpm. Because spatial inhomogeneities in the refractoriness play an important role in tachycardia-induced remodeling,\textsuperscript{14,15} to grossly determine whether these changes in the mRNA levels have regional inhomogeneities, the mRNA levels with a pacing rate of 1200 bpm were compared between the right and left atrial appendages. However, no significant differences were observed between the right and left atrial appendages, although this result could not deny the presence of regional differences in smaller areas. These results indicated that the alterations in the mRNA levels of these genes could be attributed to the effects of high-rate excitation.

**Western Blot Analysis**

To determine whether there were changes in channel protein expression corresponding to the changes in the mRNA levels, Western blot analysis was performed by using antibodies to Kv1.5, Kv2.1, Kv4.2, and Kv4.3 channel protein (Figure 5). Kv2.1 was maintained stable in the membrane fraction during 8-hour rapid pacing, corresponding to the findings for its mRNA level. In contrast, the Kv1.5 channel protein significantly increased with rapid pacing. The anti-Kv1.5 antibody recognized 2 bands (75 and 60 kDa) as reported previously.\textsuperscript{12} Although it is yet unknown whether the smaller protein represents the isoform or the breakdown of the intact protein, the amount of the 2 bands increased similarly. The increase was significant at 2 through 8 hours. However, the protein level began to decline after 4 to 8 hours ($P<0.05$). The protein levels of Kv4.2 and Kv4.3 both tended to decrease at 8 hours after the onset of pacing, although the changes were not statistically significant. These changes in the protein levels almost coincided with changes in the mRNA levels of Kv1.5, Kv4.2, and Kv4.3.

**Electrophysiological Study**

To determine whether the increased level of the Kv1.5 channel protein is reflected in the electrophysiological properties of the atrium, MAPs were recorded from the atrium paced for 4 hours, when the Kv1.5 protein level was considered to be maximum, and compared with MAPs from the sham-operated atrium. Because rapid pacing is known to shorten the action potential duration physiologically, the hearts were maintained at sinus rhythm for 30 minutes after the isolation. MAP duration (90\% repolarization) was significantly shorter in the rapidly paced atrium than in the sham-operated atrium (Figure 6). To determine whether the shortening could be attributed to the increased expression of the Kv1.5 channel, the effects of a low concentration (300 $\mu$mol/L) of 4-aminopyridine (4-AP), a relatively specific blocker of Kv1.5,\textsuperscript{16} on MAP duration were examined.

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**Figure 3.** Time course of the effects of rapid pacing at a rate of 1200 bpm on mRNA levels of Kv1.5, Kv4.2, and Kv4.3. Top panels, Results of RNase assay (Kv1.5, Kv4.2, and Kv4.3) are shown. Numbers indicate time (hours) after onset of rapid pacing; C, sham-operated animals; and N, negative control with yeast tRNA. Lines and circles represent protected fragments of channel gene and cyclophilin, respectively. mRNA level of Kv1.5 was immediately and transiently increased by rapid pacing and returned to baseline value at 8 hours, whereas mRNA levels of Kv4.2 and Kv4.3 gradually and progressively decreased (all $P<0.05$ by ANOVA). Bottom panel, Percent change vs baseline in each mRNA level is shown as mean±SD (n=5, *$P<0.05$ vs baseline).
The drug almost abolished the difference in MAP duration between the rapidly paced and sham-operated hearts, suggesting that the increased expression of the Kv1.5 channel protein was functioning in relation to the shortening of MAP.

**Discussion**

**Major Findings**

The major findings of the present study are as follows: (1) even short-term high-rate atrial pacing can modify the mRNA levels of 3 voltage-dependent K⁺ channel genes, (2) the time course and the magnitude of the changes in these mRNA levels are different (for Kv1.5, an immediate and transient increase; for Kv4.2 and Kv4.3, a gradual and progressive decrease), but all were rate dependent, and (3) the Kv1.5 channel protein significantly increased in the membrane fraction and shortened the action potential duration, corresponding to the change in its mRNA levels.

**Electrophysiological Changes by Short-Term AF**

Some investigators have observed an electrophysiological response of atrial refractoriness to short-term AF in humans and experimental animals.³,⁴,¹⁴,¹⁵ In humans, paroxysmal AF for a short period of ≈7 minutes decreased the atrial refractoriness immediately.³,⁴ This decrease is considered to result from functional responses of ion channels, including L-type Ca²⁺ current or delayed rectifier K⁺ current, and not to be related to modified gene expression in ion channels.³,⁴

Apart from very short AF sustained only for several minutes, the effects of several-hour AF on the atrial electrophysiological characteristics have not been well clarified. In an experimental canine model,¹⁷ the effects of 7-hour pacing on atrial refractoriness have been reported. The pacing decreased the refractoriness quickly (within 30 minutes after its onset) and, thereafter, shortened it with a more gradual time course during the subsequent hours. In the present study, atrial refractoriness did not reach the baseline value within 30 minutes after the cessation of pacing; these findings were different from those in several-minute AF. Similar results have been reported for 24-hour rapid pacing in goats⁵,¹⁸; the shortening and recovery of the atrial refractoriness showed an exponential time course of several hours, not several minutes. These findings suggest that several-hour rapid pacing might lead to biochemical electrical remodeling that does not recover rapidly and lead to the hypothesis that the electrophysiological changes of the atrium may differ for short-term (several-minute) and intermediate-term (several-hour) rapid pacing. The present results provided the molecular evidence that these late-phase gradual changes of the atrial refractoriness in several-hour rapid pacing might result from changes in the gene expression of ion channels. The mRNA and...
protein levels of the Kv1.5 gene that presumably encodes the ultrarapid delayed rectifier current (\(I_{\text{kur}}\))\(^{16,19}\) could increase rapidly and transiently by rapid pacing, which may contribute, at least in part, to the shortening of refractoriness.

Actually, in our model, the action potential duration was significantly shorter for the rapidly paced hearts than for the sham-operated hearts, even after a recovery period of 30 minutes, when the functional response to \(\text{Ca}^{2+}\) overload should be recovered. The shortening was almost abolished by a low concentration of 4-AP, a relatively specific blocker of Kv1.5.\(^{16}\) These results were compatible with a notion that the increased Kv1.5 channel protein causes the biochemically based electrical remodeling.

**Relevance to Electrical Remodeling by Long-Term (Chronic) AF**

Different from short-term rapid pacing, the electrical remodeling in long-term AF results from the altered gene expression of several ion channels.\(^{6-8,20}\) The density of L-type \(\text{Ca}^{2+}\) current decreases progressively in canine atria, which would explain, for the most part, the shortening and the maladaptation to rate of the atrial refractoriness demonstrated in chronic AF.\(^{7}\) Moreover, the \(\text{Ca}^{2+}\)-insensitive \(I_{\text{to}}\) is reported to decrease with a similar time course.\(^{6,7}\) Because the decrease of \(I_{\text{to}}\) density was functionally evident after 24-hour pacing,\(^{7}\) the mRNA levels of the channels encoding \(I_{\text{to}}\), which are thought to be Kv4.3 in dogs and humans and Kv4.2 and Kv4.3 in rats,\(^{10,21}\) should decrease before the decline of the current density. The present observations involving the Kv4.2 and Kv4.3 mRNA levels would support this notion that the molecular events triggering the \(I_{\text{to}}\) decrease could start during several-hour atrial tachycardia, although the mRNA levels do not always correspond to their protein levels.\(^{10,22}\)

Conversely, the density of \(I_{\text{Kur}}\) that is encoded by Kv1.5\(^{18}\) has never been reported to increase in long-term AF. In canine hearts, the density of \(I_{\text{Kur}}\) is maintained stable between 0 and 42 days of rapid pacing.\(^{7}\) In chronic human AF, the density of \(I_{\text{Kur}}\) (sustained component of IK) and Kv1.5...
protein levels were reported to decrease significantly. Although these results seemed to contradict the present observations, this inconsistency may be explainable, because the increase of Kv1.5 protein in intermediate-term tachycardia was transient, peaking at ~4 hours after the onset of pacing. Actually, the mRNA level of Kv1.5 returned to the baseline level after 8 hours of pacing. Consequently, the Kv1.5 protein level might return to the baseline level during long-term atrial tachycardia. In human data, the decrease in Kv1.5 protein was observed in chronic atrial fibrillation for a much longer period.

Possible Explanations
The mRNA level of the Kv1.5 gene has been shown to be immediately modulated by several kinds of stimuli. In rat ventricular myocytes, the mRNA level is immediately increased by K⁺ depolarization, glucocorticoids, and increased intracellular calcium. Also, in rat neonatal atrial myocytes, the level is increased by K⁺ depolarization as early as 1 hour after depolarization. Interestingly, this immediate and transient nature was quite similar to the observation of the mRNA level of Kv1.5 in the present model, in which frequent depolarizations were induced by rapid pacing. Therefore, similar depolarization-induced mechanisms may be possible on the basis of the pacing rate–dependent increase of its mRNA level, although hemodynamic effects that exhibited the rate dependence of atrial pressure may be involved.

Study Limitations
The present study has several limitations. First, the actual current density of $I_{Ks}$ could not be examined. Considering the immediate and transient change of Kv1.5 mRNA and protein levels, the turnover of the transcript/protein would be very rapid (within only 2 hours), making it difficult to measure the transient change of the current density by the patch-clamp method. Moreover, it should be recognized that the isolation procedure of single myocytes itself would modify the gene expression immediately, because perfusion with Ca²⁺–free Tyrode’s solution would have an effect totally opposite the effect of the rapid pacing. Second, although 4-AP is known to inhibit $I_{Ks}$, in a small concentration in canine and human myocytes (IC$_{50}$ ≈ 50 μmol/L), the dose-response relation was somewhat different for rat Kv1.5 (IC$_{50}$ = 600 μmol/L). Therefore, the significance of the transient increase of the Kv1.5 channel protein could not be definitely demonstrated without a Kv1.5-specific inhibitor. Third, even if the short-term tachycardia increased the Kv1.5 channel gene expression, its significance in arrhythmogenesis remains unclear. Moreover, it should be specifically mentioned that the increased expression, being transient, applies only to the initial hours after the initiation of atrial tachycardia. Last, because the regulation of ion channel expression might be different among species, the present results cannot be applied to humans.

References


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