Ion Channel Remodeling Is Related to Intraoperative Atrial Effective Refractory Periods in Patients With Paroxysmal and Persistent Atrial Fibrillation

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Background—Sustained shortening of the atrial effective refractory period (AERP), probably due to reduction in the L-type calcium current, is a major factor in the initiation and maintenance of atrial fibrillation (AF). We investigated underlying molecular changes by studying the relation between gene expression of the L-type calcium channel and potassium channels and AERP in patients with AF.

Methods and Results—mRNA and protein expression were determined in the left and right atrial appendages of patients with paroxysmal (n = 13) or persistent (n = 16) AF and of 13 controls in sinus rhythm using reverse transcription polymerase chain reaction and slot-blot, respectively. The mRNA content of almost all investigated ion channel genes was reduced in persistent but not in paroxysmal AF. Protein levels for the L-type Ca\(^{2+}\) channel and 5 potassium channels (Kv4.3, Kv1.5, HERG, minK, and Kir3.1) were significantly reduced in both persistent and paroxysmal AF. Furthermore, AERPs were determined intraoperatively at 5 basic cycle lengths between 250 and 600 ms. Patients with persistent and paroxysmal AF displayed significant shorter AERPs. Protein levels of all ion channels investigated correlated positively with the AERP and with the rate adaptation of AERP. Patients with reduced ion channel protein expression had a shorter AERP duration and poorer rate adaptation.

Conclusions—AF is predominantly accompanied by decreased protein contents of the L-type Ca\(^{2+}\) channel and several potassium channels. Reductions in L-type Ca\(^{2+}\) channel correlated with AERP and rate adaptation, and they represent a probable explanation for the electrophysiological changes during AF. (Circulation. 2001;103:684-690.)

Key Words: fibrillation ■ atrium ■ ion channels ■ remodeling ■ electrophysiology

Atrial fibrillation (AF) is a common arrhythmia affecting millions of people worldwide.\(^1\) AF has the tendency to become more persistent and increasingly difficult to treat over time. During recent years, experimental and human studies showed that rapid shortening of the atrial effective refractory period (AERP) is an important factor contributing to the maintenance of AF\(^2-4\) and involves functional changes in ion channels. Animal experimental data revealed that the L-type Ca\(^{2+}\) channel plays an important role in shortening the AERP and action potential duration.\(^5,6\) These observations were supported by the blocking of AERP shortening with the L-type Ca\(^{2+}\) antagonist verapamil in other experimental studies.\(^7,8\) In addition, human data on AF have demonstrated reductions in I\(_{Ca}\)\(^{9,10}\) and the gene expression of the L-type Ca\(^{2+}\) channel.\(^11\)

However, AERP shortening could also be explained by an increase in (repolarizing) K\(^+\) channel activity. Indeed, one study found increased I\(_{K_{ACs}}\) and I\(_{K_{i}}\) in the isolated, human, atrial cells of patients with persistent AF.\(^9\) In contrast, other studies support decreases in K\(^+\) channels in AF. In human atrial myocytes, reductions in I\(_{Na}\) and I\(_{K_{suv}}\) and reduced gene expression of several potassium channels (Kv1.5, Kv4.3, Kir3.1, Kir3.4, and Kir6.2)\(^11-13\) were found.

Until now, the relationship between changes in AERP and ion channel gene expression has not been investigated in the human tissue of patients with AF. The aim of the present study was to investigate the regulation of the L-type Ca\(^{2+}\) channel and K\(^+\) channels and their relation to AERP in patients with persistent and paroxysmal AF. We included patients with lone AF and with mitral valve disease (MVD), because the occurrence of MVD seems to prolong the AERP.\(^14\)

Methods

Patients and Atrial Tissue Collecting

Before surgery, one investigator assessed the clinical characteristics of patients (Table 1), as described previously.\(^11\) The persistent and...
TABLE 1. Baseline Characteristics of Patients With Paroxysmal AF or Persistent AF and of Control Patients in Sinus Rhythm

<table>
<thead>
<tr>
<th></th>
<th>Lone AF</th>
<th>PAF</th>
<th>CAF</th>
<th>SR (MVD)</th>
<th>PAF</th>
<th>CAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±8</td>
<td>48±7</td>
<td>50±7</td>
<td>60±9</td>
<td>47±9</td>
<td>56±10</td>
</tr>
<tr>
<td>Previous duration of AF, m</td>
<td>—</td>
<td>—</td>
<td>13.6(0.1–56)</td>
<td>—</td>
<td>—</td>
<td>8(0.4–32)</td>
</tr>
<tr>
<td>Duration of SR before surgery, d</td>
<td>—</td>
<td>2(0.5–12)</td>
<td>—</td>
<td>—</td>
<td>75(10–210)</td>
<td>—</td>
</tr>
<tr>
<td>Underlying heart disease/surgical procedure, n</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Coronary artery disease/CABG</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lone AF/MAZE</td>
<td>0</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MVD/MAZE replacement/repair</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>New York Heart Association class for exercise tolerance</td>
<td>—</td>
<td>—</td>
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<td>3</td>
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<tr>
<td>III</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial diameter (parasternal), mm</td>
<td>36±5</td>
<td>39±5</td>
<td>45±8</td>
<td>47±5</td>
<td>45±9</td>
<td>51±10</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter, mm</td>
<td>37±7</td>
<td>50±4</td>
<td>49±8</td>
<td>60±7</td>
<td>54±8</td>
<td>54±5</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter, mm</td>
<td>29±8</td>
<td>37±4</td>
<td>29±13</td>
<td>38±6</td>
<td>38±6</td>
<td>38±7</td>
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<tr>
<td>Medication, n</td>
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<td>1</td>
<td>4</td>
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<td>0</td>
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<td>Verapamil</td>
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<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD, median (range), or number of patients. ACE indicates angiotensin-converting enzyme; CAF, chronic, persistent atrial fibrillation; PAF, paroxysmal atrial fibrillation; and SR, control patients in sinus rhythm.

RNA Isolation and cDNA Synthesis
Total RNA was isolated and processed as described previously.11 Briefly, cDNA was synthesized by incubating 1 μg of RNA in reverse transcription buffer, 200 ng of random hexamers with 200 U of Moloney Murine Leukemia Virus Reverse Transcriptase, 1 mmol/L of each dNTP, and 1 U of RNase inhibitor (Promega). Synthesis reaction was performed for 10 minutes at 20°C, 20 minutes at 42°C, 5 minutes at 99°C, and 5 minutes at 4°C. All products were checked for contaminating DNA.

Semiquantitative Polymerase Chain Reaction Analyses
We described and validated the methods used previously.11 In short, the cDNA of interest and of the ubiquitously expressed housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were coamplified in a single polymerase chain reaction (PCR). Primers (Eurogentec) were designed for SCNA1, L-type calcium channel α1C, Kv4.3, HERG, Kv1.5, Kir3.4, KvLQT1, Kir6.2, and GAPDH (Table 2).

The PCR products were separated on an agarose gel by electrophoresis and stained with ethidium bromide. The density of the PCR products was quantified by densitometry. Linearity of PCR was established by a correlation between number of cycles and density of gene of interest and GAPDH (data not shown).

Protein Preparation and Slot Blotting
Frozen atrial appendages of all patients were homogenized in RadioImmunoPrecipitationAssay buffer, as described previously.11 The homogenate was centrifuged at 14 000 rpm for 20 minutes at 4°C. The supernatant was used for protein concentration measurement according to the Bradford method (Bio-Rad). Samples of 10 μg of heat-denatured protein were spotted on nitrocellulose membranes (Stratagene) and checked by staining with Poncet S solution (Sigma). Blocking the membranes (in 5% nonfat milk, Tris-buffered saline, and 0.1% Tween 20) was followed by incubation with the primary antibodies against GAPDH (Affinity Reagents), L-type calcium channel α1C subunit, Kv4.3, HERG, minK, Kir3.1, or Kv1.5 (all Alomone Labs). Immunodetection of the primary antibody was performed with peroxidase-conjugated secondary antibody anti-mouse IgG (Santa Cruz Biotechnology). Blots were incubated with enhanced chemiluminescence–detection reagent (Amersham) for 1 minute and exposed to X-OMAT x-ray films (Kodak) for 15 to 90 seconds. Band densities were evaluated by densitometric scanning using a Snap Scan 600 (Agfa). The amount of protein chosen was in the linear immunoreactive signal area, and the specificity of
the antibody was checked by SDS-PAGE and preincubation with control peptide antigen.

Rate Adaptation Coefficient
To quantify the change in AERP at different BCLs, we calculated the rate adaptation coefficient for every RAA and LAA as the slope of the linear regression after logarithmic transformation of BCL. Three patients were excluded because their AERPs were obtained at 4 BCLs.

Statistical Analysis
All PCR and slot-blotting procedures were performed in duplicate, and mean values were used for statistical analysis. Comparison between groups for normally distributed variables was performed by 1-way ANOVA and for skewed variables by Wilcoxon 2-sample test. For determination of correlations, the Spearman correlation test was used. The Mann-Whitney U-test was performed for group to group comparisons of small numbers. All probability values are 2-sided; \( P \leq 0.05 \) was considered statistically significant. SPSS version 8.0 was used for all statistical evaluations.

Results
mRNA Remodeling
Changes in transcription were determined by a comparison of gene-of-interest/GAPDH ratios between patients with persistent AF, paroxysmal AF, and their controls in sinus rhythm (Table 3). No differences in GAPDH amount between the groups were found for all the genes investigated (data not shown). Persistent, lone AF was associated with reductions in mRNA amount of Kv4.3, L-type Ca\(^{2+}\) channel, and Kir3.4.

The mRNA amounts of HERG, KvLQT1, and Kir6.2 showed additional changes in persistent AF with MVD. In addition, significant changes in mRNA amount were found in patients with paroxysmal AF but, in general, these changes were less pronounced compared with those in patients with persistent AF (Table 3).

Protein Remodeling
Proteins were isolated from the RAA and LAA and used for immunological detection of L-type Ca\(^{2+}\) channel, voltage-gated L-type calcium channel \( \alpha_{1C} \) subunit; Kv4.3, gene probably encoding the calcium-independent transient outward current \( \iota_{\text{to1}} \); KvLQT1, gene encoding the slow delayed rectifier current together with minK; HERG, gene encoding the rapid component of the delayed rectifier; Kv1.5, gene encoding the ultrarapid component of the delayed rectifier \( \iota_{\text{Kur}} \); Kir3.4, gene encoding part of the heterotetrameric complex of this gene together with Kir3.1, which forms the acetylcholine-dependent potassium current \( \iota_{\text{KAC}} \); and Kir6.2, gene encoding the inward rectifier K\(^{+}\) current, forming \( \iota_{\text{KATP}} \) with sulfonylurea receptor 2.

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The AERP at 5 different BCLs (600, 500, 400, 300, and 250 ms) was determined in the RAA and LAA of patients during surgery. The overall persistent and paroxysmal AF patients had significantly shorter AERPs than patients in sinus rhythm (Table 4). The relation between AERP and the amount of ion channel protein was investigated because protein amounts are thought to represent the amount of functional ion channel better than mRNA levels. A significant, positive correlation was found at BCLs of 600, 500, 400, and 300 ms for all the proteins investigated in patients with AF (Figure 2 and Table 5). Patients with reduced ion channel protein expression exhibited the shortest AERPs. Furthermore, no significant correlation was found between the GAPDH amount and AERP, and correlations were not different between the lone AF group and AF with MVD group (data not shown).

**Relation Rate Adaptation and Protein Remodeling**

The rate adaptation coefficient was determined for every RAA and LAA. The rate adaptation coefficient was significantly reduced by 32% in patients with persistent AF compared with those in sinus rhythm (mean in persistent AF, 104±53; paroxysmal AF, 133±62; and sinus rhythm, 153±32), indicating a poorer adaptation to higher heart rates in patients with AF (Table 4). Significant positive correlations were observed between ion channel protein expression and the adaptation coefficient (Figure 3). AF patients with reduced ion channel protein expression demonstrated poorer rate adaptation.

Furthermore, significant differences were observed between patients with lone paroxysmal AF and patients with paroxysmal AF and MVD. Those with lone paroxysmal AF demonstrated a poorer rate adaptation compared with those with paroxysmal AF with MVD (109±38 and 149±49, respectively, P=0.04; Table 4).

**Discussion**

Both experimental and human AF is accompanied by electrical remodeling and ion channel remodeling. This is the first study to demonstrate (1) a positive correlation between ion channel protein remodeling and the AERP in human paroxysmal and persistent AF, irrespective of the underlying heart disease; (2) a correlation between ion channel protein remodeling and changes in rate adaptation; and (3) discrepancies between mRNA and protein remodeling. These data suggest that ion channel protein remodeling...
TABLE 3. Ion-Channel Remodeling: Percentage Change in Ion-Channel Protein Expression in Patients With Lone AF and AF With MVD Compared With Controls in Sinus Rhythm

<table>
<thead>
<tr>
<th>mRNA</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na channel</td>
<td>Lone PAF</td>
</tr>
<tr>
<td></td>
<td>Lone PAF</td>
</tr>
<tr>
<td>Na channel</td>
<td>35 ± 6</td>
</tr>
<tr>
<td>Kv4.3</td>
<td>-20 ± 4</td>
</tr>
<tr>
<td>L-type Ca2+ channel</td>
<td>-13 ± 5</td>
</tr>
<tr>
<td>HERG</td>
<td>NS</td>
</tr>
<tr>
<td>Kv1.5</td>
<td>NS</td>
</tr>
<tr>
<td>KvLQT1/minK</td>
<td>NS</td>
</tr>
<tr>
<td>Kir3.1/minK</td>
<td>NS</td>
</tr>
<tr>
<td>Kir6.2</td>
<td>28 ± 4</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Only significant changes (P < 0.05) are given for the mRNA or protein content of interest/GAPDH. CAF indicates patients with chronic, persistent AF; PAF, paroxysmal AF; NS, not significant; and NA, not available.

*Significant differences between lone PAF and PAF with MVD or lone CAF and CAF with MVD.

Table 3. Ion-Channel Remodeling: Percentage Change in Ion-Channel Protein Expression in Patients With Lone AF and AF With MVD Compared With Controls in Sinus Rhythm

represents an important adaptation mechanism during AF that may contribute to the intractability of AF and the inefficiency of antiarrhythmic drugs instituted for the prevention of AF.

Relation of Ion Channel Remodeling and AERP

The observed ion channel protein remodeling in this study is associated with the occurrence of AF. Patients with paroxysmal and persistent AF showed marked reductions in ion channel protein expression of the L-type Ca2+ channel and several K+ channels. Furthermore, low ion channel protein levels were associated with short AERPs and poor rate adaptation. This indicates that electrical remodeling2 and structural remodeling16 are paralleled by ion channel protein remodeling as part of the adaptation mechanisms during AF. Furthermore, patients with paroxysmal AF showed a reduction in ion channel protein expression comparable to persistent AF in the absence of mRNA reductions, suggesting that paroxysms of AF are able to induce changes in ion channel protein expression via the activation of a proteolytic system. Indeed, we have observed the activation of the calpain system in human paroxysmal and persistent AF (B.J.J.M. Brundel, MSc, et al, unpublished data, 2000).

As stated above, AF is accompanied by a shortening of the AERP and action potential duration. It has been suggested that the short-term decrease of action potential duration and its reduced rate adaptation is mainly due to a ≥70% reduction of the L-type calcium current.5,6,9,10 If the main role for L-type Ca2+ channels in action potential duration is correct, the observed reductions in protein expression of L-type Ca2+ channel in this study explain the present AERP shortening and decrease in its adaptation to rate.

The other possibility that may mediate AERP shortening is an increase in (repolarizing) K+ channel gene products and/or activity. However, we observed a reduction of K+ channel gene expression. Similar results were obtained in animal experimental studies showing reductions in Ito and Kv4.3 mRNA amount.5 Van Wagoner et al10,13 and our group11,12 examined the adaptation in gene expression of several potassium channels in patients with AF. The Ito current and the protein expression of Kv1.5 were reduced rather than elevated during persistent AF.13 Our previous study in a different patient group showed reductions in gene expression of Kv4.3, Kv1.5, Kir3.1, and Kir6.2.12 Only one study in the isolated RAA cells of patients with persistent AF showed that shortening of the human action potential by AF was related to a 70% reduction in Ito and a 30% increase in Ito.9 The downregulation of potassium channel protein...
amounts observed in our study is in contrast with these results on the electrophysiological level and may be explained by a change in single-channel properties in patients with persistent AF, such as an increase of mean open-time, an increase in channel conductance, or a change in voltage dependency. Thus, a reduced expression of L-type Ca\(^{2+}\) channels probably plays a major role in AERP shortening. Secondary to this process, the myocardial cell may further adapt to high rate by reducing the expression of potassium channels to counteract the shortening of the AERP.

We did not find differences in ion channel protein expression between AF patients with lone AF and those with AF with underlying MVD. Nevertheless, AERP was prolonged in patients with MVD, as was previously reported in experimental studies.\(^ \text{14} \) In addition, an association between AF with MVD and severe cellular degeneration was observed.\(^ \text{17} \) The results indicate that other factors besides AF are probably involved in the regulation of the duration of the effective refractory period. One of the most likely candidates would be morphological changes, because AF is promoted by structural changes induced during experimental heart failure that cause important local conduction abnormalities that could play an additional role in the vulnerability of AF.\(^ \text{18} \)

**Post-Transcriptional Regulation?**

The observed discrepancy between alterations in mRNA and protein expression in patients with paroxysmal AF suggests the activation of proteolysis. Recently, we found that the calpain system was activated in human persistent and paroxysmal AF in the absence of proteasome pathway activation (B.J.J.M. Brundel, MSc, et al, unpublished data, 2000). Because calpain is activated by calcium overload in the myocardial cell,\(^ \text{19} \) calpain activation would serve to protect cells from additional damage by downregulation of multiple ion channels. However, this would be at the cost of proteolysis of several cytoskeletal, membrane-associated, and regulatory proteins.\(^ \text{20,21} \) Whether interference with the calpain system represents a valuable therapeutic strategy in AF remains to be investigated.

In conclusion, the observed correlation between ion channel protein amounts and AERP strongly suggest that ion channel protein remodeling, in addition to electrical remodeling and structural remodeling, may play an important role in the vulnerability of AF after restoration of sinus rhythm.

**Limitations of the Study**

The patients with lone AF included in this study represent patients who were difficult to treat and finally underwent MAZE surgery. Therefore, the present data cannot be extrapolated uncritically to all patients with AF. It should be noted that in all groups, the number of patients was small, and drugs could affect the ion channel protein expression. Because regional differences in tachycardia-induced AERP changes were found,\(^ \text{22} \) the described results should be carefully extrapolated to the whole atrium.

**Acknowledgments**

Dr Van Gelder was supported by grant 94.014 from the Netherlands Heart Foundation, The Hague, The Netherlands. The study was

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**TABLE 4. AERP Measured at the Different BCLs and the Rate Adaptation Coefficient**

<table>
<thead>
<tr>
<th>BCL, ms</th>
<th>Lone AF</th>
<th>AF With MVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SR (CABG)</td>
<td>PAF</td>
</tr>
<tr>
<td>600 ms</td>
<td>291±53</td>
<td>222±15*</td>
</tr>
<tr>
<td>500 ms</td>
<td>277±42</td>
<td>224±24*</td>
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<td>400 ms</td>
<td>252±34</td>
<td>216±24*</td>
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<tr>
<td>300 ms</td>
<td>224±16</td>
<td>202±20*</td>
</tr>
<tr>
<td>250 ms</td>
<td>184±5</td>
<td>185±19</td>
</tr>
</tbody>
</table>

Adaptation coefficient: 138±33 109±38 87±57* 168±26 149±49 125±38*

---

**TABLE 5. Relation of AERP and Protein Remodeling for Different BCLs**

<table>
<thead>
<tr>
<th>BCL, ms</th>
<th>L-type Ca(^{2+}) Channel</th>
<th>Kv4.3</th>
<th>Kv1.5</th>
<th>HERG</th>
<th>Kir3.1</th>
<th>minK</th>
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<tr>
<td>600 ms</td>
<td>0.67</td>
<td>0.001</td>
<td>0.32</td>
<td>0.001</td>
<td>0.57</td>
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<tr>
<td>500 ms</td>
<td>0.77</td>
<td>&lt;0.001</td>
<td>0.43</td>
<td>&lt;0.001</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>400 ms</td>
<td>0.68</td>
<td>&lt;0.001</td>
<td>0.35</td>
<td>0.004</td>
<td>0.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>300 ms</td>
<td>0.53</td>
<td>&lt;0.001</td>
<td>0.29</td>
<td>0.04</td>
<td>0.47</td>
<td>0.009</td>
</tr>
<tr>
<td>250 ms</td>
<td>0.47</td>
<td>0.001</td>
<td>NS</td>
<td>NS</td>
<td>0.42</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. Abbreviations as in Table 1. \(*P<0.05\) compared with controls in sinus rhythm.
supported by grant 96.051 from The Netherlands Heart Foundation, The Hague, The Netherlands.

References
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