Atrial L-Type Ca\textsuperscript{2+} Currents and Human Atrial Fibrillation

David R. Van Wagoner, Amber L. Pond, Michelle Lamorgese, Sandra S. Rossie, Patrick M. McCarthy, Jeanne M. Nerbonne

Abstract—Chronic atrial fibrillation (AF) is characterized by decreased atrial contractility, shortened action potential duration, and decreased accommodation of action potential duration to changes in activation rate. Studies on experimental animal models of AF implicate a reduction in L-type Ca\textsuperscript{2+} current (I\textsubscript{Ca}) density in these changes. To evaluate the effect of AF on human I\textsubscript{Ca}, we compared I\textsubscript{Ca} in atrial myocytes isolated from 42 patients in normal sinus rhythm at the time of cardiac surgery with that of 11 chronic AF patients. I\textsubscript{Ca} was significantly reduced in the myocytes of patients with chronic AF (mean \(-3.35\pm0.5\) pA/pF versus \(-9.13\pm1.0\) pA/pF in the controls), with no difference between groups in the voltage dependence of activation or steady-state inactivation. Although I\textsubscript{Ca} was lower in myocytes from the chronic AF patients, their response to maximal \(\beta\)-adrenergic stimulation was not impaired. Postoperative AF frequently follows cardiac surgery. Half of the patients in the control group (19/38) of this study experienced postoperative AF. Whereas chronic AF is characterized by reduced atrial I\textsubscript{Ca}, the patients with the greatest I\textsubscript{Ca} had an increased incidence of postoperative AF, independent of patient age or diagnosis. This observation is consistent with the concept that calcium overload may be an important factor in the initiation of AF. The reduction in functional I\textsubscript{Ca} density in myocytes from the atria of chronic AF patients may thus be an adaptive response to the arrhythmia-induced calcium overload. (Circ Res. 1999;85:428-436.)

Key Words: atrial fibrillation ■ postoperative atrial fibrillation ■ Ca\textsuperscript{2+} channel ■ \(\beta\)-adrenergic antagonist ■ cardiac surgery

Atricular fibrillation (AF) is the most common chronic arrhythmia, afflicting nearly 2 million Americans. In spite of a growing recognition of its prevalence and associated morbidity and mortality, the mechanisms involved in the initiation, maintenance, and termination of AF remain poorly understood. Altered action potential characteristics (decreased response to verapamil and decreased resting potential) were noted in microelectrode recordings from diseased and fibrillating atrial tissue in 1976. More than a decade ago, a shortening of the effective refractory period and diminished adaptation to changes in rate were demonstrated in patients vulnerable to the development of AF. In microelectrode recordings from atrial tissue removed from chronic AF patients, a later study demonstrated a similar loss of rate adaptation and concomitant shortening of atrial action potential duration. In 1995, Wijffels et al demonstrated that initiation of AF in electrically stimulated goat atria caused consistent and relatively rapid electrophysiological changes. This pivotal study rekindled scientific interest in identifying the mechanisms involved in the initiation of AF, as well as the mechanisms responsible for the adaptation of the atria to the high-rate rhythm.

To evaluate the cellular mechanism(s) responsible for these changes, we previously evaluated the hypothesis that an increased density of repolarizing K\textsuperscript{+} currents in the atrial myocytes of chronic AF patients could explain the reported electrophysiological changes. In contrast to this hypothesis, the densities of both the transient and sustained outward K\textsuperscript{+} currents were found to be significantly reduced in myocytes from chronic AF patients, combined with a decreased expression of the Kv1.5 K\textsuperscript{+} channel protein. To explain this result, we inferred that the reduction in action potential duration was most likely the result of a simultaneous greater reduction in the density of voltage-dependent L-type Ca\textsuperscript{2+} current (I\textsubscript{Ca}). A reduction in I\textsubscript{Ca} has been documented in the rapidly paced canine atria.

Since the publication of our initial results, several studies have reported that the electrophysiological remodeling accompanying episodes of AF could be prevented by pretreatment with calcium channel blockers, suggesting that calcium overload was a critical factor in the electrophysiological remodeling process. Calcium overload might initiate the changes in gene expression that eventually lead to a down-regulation of atrial K\textsuperscript{+} and Ca\textsuperscript{2+} current densities.

In the rapidly paced canine atria model of AF, there has been shown to be both a decrement in functional I\textsubscript{Ca} and a decrease in the number of dihydropyridine binding sites. In...
recent studies on patients with AF, it has been demonstrated that both mRNA\textsuperscript{11,12} and protein\textsuperscript{12} for the L-type Ca\textsuperscript{2+} channel are reduced in patients with established AF. However, there has been no systematic evaluation of the functional L-type Ca\textsuperscript{2+} current density in patients with AF. The goal of the present study was to directly evaluate and compare the density of \(I_\text{Ca}\) in myocytes from patients in normal sinus rhythm with that of myocytes from chronic AF patients undergoing the Maze procedure for surgical treatment of the arrhythmia. Because of the implicit link between calcium overload and the initiation of electrophysiological remodeling, we also sought to analyze the relationship between preoperative \(I_\text{Ca}\) and the subsequent development of postoperative AF.

Materials and Methods

Patient Population

Atrial myocytes in the present study were isolated from the atrial appendage of 3 distinct patient groups: (1) patients in normal sinus rhythm undergoing first-time coronary artery bypass graft and/or valve repair surgery (\(n=40\)); (2) nonfailing hearts from unmatched organ donors in normal sinus rhythm (\(n=3\)); and (3) chronic AF patients undergoing the Maze III surgery (\(n=14\)). The study protocol was approved by the Cleveland Clinic Foundation Institutional Review Board. Experiments were performed from January 1997 to May 1999. Tissue from group 1 patients was excised from the tip of the right atrial appendage at the time of bypass cannulation, placed in saline, and taken to the laboratory. Similarly, atrial appendages from group 3 patients were excised, placed in saline, and brought to the laboratory. Hearts from group 2 patients were perfused with cardioplegia before removal, chilled, and returned to the laboratory (within \(\approx 1\) hour of explant). Clinical characteristics of the control patients (groups 1 and 2) are summarized in Table 1, along with a notation about their subsequent status with respect to the development of postoperative AF. Clinical characteristics of the chronic AF patients are summarized in Table 2.

Atrial Myocyte Isolation Protocol

Atrial myocytes were dissociated using the protocol previously described,\textsuperscript{6} with one change in the composition of the dissection buffer (DB). The DB in the present study contained (mmol/L) sucrose 134, NaCl 35, NaHCO\textsubscript{3} 25, Na\textsubscript{2}HPO\textsubscript{4} 16, KCl 4.75, KH\textsubscript{2}PO\textsubscript{4} 1.2, HEPES 10, and glucose 10 (pH 7.4) with NaOH. The myocytes were kept oxygenated at room temperature until used, within 8 hours of isolation. Yields were in the range of 10% to 40% for viable calcium-tolerant myocytes. Only well-striated, rod-shaped myocytes were used in the electrophysiological studies.

Conventional Whole-Cell Patch-Clamp Technique

Conventional (ruptured patch) recording techniques were used to measure whole-cell \(I_\text{Ca}\). The pipette solution contained (mmol/L) CsCl 125, tetraethylammonium chloride (TEA-Cl) 20, MgATP 5, creatine phosphate 3.6, EGTA 10, and HEPES 10 (pH 7.2) with CsOH. The bath solution contained (mmol/L) TEA-Cl 157, CaCl\textsubscript{2} 1, MgCl\textsubscript{2} 0.5, and HEPES 10 (pH 7.4) with CsOH. The junction potential with these solutions was 7.5 mV (calculated using Axoscope, version 1.1, Axon Instruments) and was not corrected.

Data were acquired using a Pentium computer that controlled data acquisition hardware and software (pClamp 6.03+, Axon Instruments) connected to either Axopatch 1C or Axopatch 200 amplifiers (Axon Instruments). Currents were filtered at 2 kHz and sampled at 4 to 10 kHz. A holding potential of \(-50 \text{ mV} \) was used to inactivate Na\textsuperscript{+} current. \(I_\text{Ca}\) was elicited with step depolarization protocols, using test potentials in the range of \(-40 \text{ to } +30 \text{ mV}\). \(I_\text{Ca}\) densities were computed by dividing current amplitudes by the whole-cell capaci-
To determine whether changes in the availability of Ca$^{2+}$ channels could account for the differences in peak $I_{\text{Ca}}$, we analyzed the steady-state inactivation characteristics in a series of myocytes from both groups (Figure 2). The voltage-clamp protocol for these experiments is shown in Figure 2A. Raw current traces from a representative control myocyte are shown in Figure 2B and from an AF myocyte in Figure 2C. The summary in Figure 2D shows that chronic AF, although lowering the peak $I_{\text{Ca}}$, had no effect on the steady-state inactivation characteristics of $I_{\text{Ca}}$ in the human atrial myocytes studied. Thus, the reduction in $I_{\text{Ca}}$ is most likely due to a decrease in the number of functionally available channels, rather than to a modification of their voltage dependence.

**Relationship Between Myocyte Capacitance and $I_{\text{Ca}}$**

The mean capacitance of the AF myocytes studied was greater than that of the control myocytes (control 67.6±2.9 pF, n=86, versus AF 90.4±8.3 pF, n=28; $P<0.01$). In Figure 3, peak $I_{\text{Ca}}$ amplitude (Figure 3A) and density (Figure 3B) for each myocyte are plotted as a function of myocyte size (capacitance). These plots illustrate that both the peak $I_{\text{Ca}}$ amplitude and density were inversely related to myocyte size. This trend was observed in myocytes from both groups of patients. Importantly, however, these plots demonstrate that the reduction in $I_{\text{Ca}}$ in the myocytes from the chronic AF patients occurred in all myocytes, regardless of capacitance. To emphasize this, Figure 3C plots the current density for control and AF myocytes for small (<60 pF), medium (60 to 100 pF), and large (>100 pF) atrial myocytes. The $I_{\text{Ca}}$ density was significantly lower in the myocytes isolated from the AF patients, relative to the controls, in each capacitance range.

**Responses to β-Adrenergic Stimulation**

The adrenergic sensitivity of patients with heart failure is reduced.$^{13,14}$ To assess whether chronic AF is similarly characterized by a diminished response to β-adrenergic stimulation, the response of individual myocytes to maximal β-adrenergic stimulation (1 μmol/L isoproterenol) was assessed in a subgroup of myocytes from both the patients in normal sinus rhythm and those in chronic AF. Figure 4 plots the mean±SEM peak $I_{\text{Ca}}$ densities for these myocytes. Isoproterenol significantly increased $I_{\text{Ca}}$ in myocytes from both the control patients (−6.6±1.4 pA/pF to −16.1±2.3 pA/pF, n=15 myocytes, from 7 patients) and the chronic AF patients (−2.6±0.6 pA/pF to −8.9±2.1 pA/pF, n=11 myocytes, from 4 patients). However, the relative response to maximal β-adrenergic stimulation (1 μmol/L isoproterenol) was greater (unpaired $t$ test, $P<0.05$) in the myocytes isolated from chronic AF patients (4.3±0.7-fold increase, n=12) compared with patients in normal sinus rhythm (2.8±0.3-fold increase, n=15). This difference remained significant (unpaired $t$ test, $P<0.01$) when the comparison was made by patient means (normal sinus rhythm 2.5±0.3 fold, n=7 patients, versus chronic AF 4.5±0.6 fold, n=4 patients).

**Effect of Chronic AF on Action Potential Duration**

Action potentials are recorded using physiological ion concentrations in both the pipette solution and the bath solution.

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**TABLE 1. Clinical Characteristics of the Patients in Normal Sinus Rhythm at the Time of Cardiac Surgery**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age, y</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Presurgical Drugs</th>
<th>Postoperative AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>M</td>
<td>CABG</td>
<td>GLY</td>
<td>−</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>M</td>
<td>CABG</td>
<td>AI</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>F</td>
<td>CABG</td>
<td>AI</td>
<td>−</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>F</td>
<td>DN</td>
<td>...</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>83</td>
<td>M</td>
<td>CABG</td>
<td>...</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>F</td>
<td>AVR/CABG</td>
<td>CC, BB</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>75</td>
<td>M</td>
<td>CABG</td>
<td>AI, CC, BB</td>
<td>−</td>
</tr>
<tr>
<td>8</td>
<td>69</td>
<td>M</td>
<td>CABG</td>
<td>BB</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>74</td>
<td>M</td>
<td>CABG</td>
<td>BB, GLY</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>M</td>
<td>CABG</td>
<td>...</td>
<td>ND</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>M</td>
<td>CABG</td>
<td>BB</td>
<td>−</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>M</td>
<td>CABG</td>
<td>BB, CC</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>M</td>
<td>AVR/CABG</td>
<td>...</td>
<td>−</td>
</tr>
<tr>
<td>14</td>
<td>74</td>
<td>M</td>
<td>CABG</td>
<td>GLY</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>73</td>
<td>M</td>
<td>CABG</td>
<td>...</td>
<td>−</td>
</tr>
<tr>
<td>16</td>
<td>67</td>
<td>F</td>
<td>CABG</td>
<td>BB</td>
<td>+</td>
</tr>
<tr>
<td>17</td>
<td>75</td>
<td>M</td>
<td>CABG</td>
<td>BB</td>
<td>−</td>
</tr>
<tr>
<td>18</td>
<td>70</td>
<td>M</td>
<td>AVR/CABG</td>
<td>BB, GLY</td>
<td>+</td>
</tr>
<tr>
<td>19</td>
<td>67</td>
<td>M</td>
<td>AVR/CABG</td>
<td>CC, BB, GLY</td>
<td>+</td>
</tr>
</tbody>
</table>

$\text{CABG}$ indicates coronary artery bypass graft; $\text{AVR}$, aortic valve repair/replacement; $\text{DN}$, nonfailing heart donor; $\text{AI}$, angiotensin-converting enzyme (ACE) inhibitor; $\text{AM}$, amiodarone; $\text{BB}$, β-adrenergic receptor blocker; $\text{CC}$, calcium channel blocker; $\text{DIG}$, digoxin; $\text{GLY}$, glybenclamide; $\text{NTG}$, nitroglycerin; $\text{N/A}$, not available; $\pm$, AF present; $-$, AF absent; $\text{ND}$, AF could not be determined; and $\text{NA}$, not applicable.
Because $I_{Ca}$ is recorded under conditions in which $K^+$ currents are strongly suppressed (CsCl in the pipette, TEA in the bath), it is not possible to quantitatively assess $I_{Ca}$ in the same myocytes from which action potentials are recorded. To qualitatively evaluate the effect of the observed changes in $I_{Ca}$ on the atrial action potential, action potentials were recorded from right atrial myocytes from patients in normal sinus rhythm and from patients in chronic AF. Figure 5A plots representative action potentials recorded over a range of cycle lengths from a myocyte isolated from a 26-year-old patient in normal sinus rhythm. A clear, cycle length–dependent variation of action potential duration is evident. To illustrate the effect of a reduction in $I_{Ca}$, Figure 5B shows action potentials from the same myocyte recorded at the same cycle lengths in the presence of 10 μmol/L nifedipine. Figure 5C plots the action potential duration at APD$_{50}$ and APD$_{90}$. In contrast, Figure 5D and Figure 5E shows action potentials recorded from atrial myocytes from 2 different chronic AF patients. Little cycle length–dependent change in action potential duration was evident, except at a 300-ms cycle length. Mean±SEM data for the APD$_{50}$ and APD$_{90}$ values of 5 myocytes isolated from 5 chronic AF patients are plotted in Figure 5F. Myocytes from chronic AF patients were characterized by shorter APD$_{50}$ values, with less variation as a function of cycle length than the control myocyte in Figure 5A. APD$_{90}$ values were also flatter across the range of cycle lengths tested.

### Relation of $I_{Ca}$ to the Occurrence of Postoperative AF

After cardiac surgery, many patients develop AF in the postoperative recovery period (typically 2 to 5 days after surgery). To determine whether the preoperative $I_{Ca}$ was correlated with the occurrence of postoperative AF, we analyzed the control patient $I_{Ca}$ recordings on the basis of the occurrence of postoperative AF during the in-hospital recovery period. Table 1 lists the clinical characteristics of the control patients and indicates whether the patient experienced postoperative AF.

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age, y</th>
<th>Sex</th>
<th>Surgery</th>
<th>AF Duration, y</th>
<th>Presurgical Drugs</th>
<th>Left Atrial Size, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>F</td>
<td>Maze/MVR</td>
<td>∼20</td>
<td>DIG, ALB</td>
<td>5.2</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>F</td>
<td>Maze/MVR/AVR</td>
<td>20</td>
<td>...</td>
<td>7.3</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>Maze/MVR</td>
<td>10</td>
<td>DIG</td>
<td>8.5</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>M</td>
<td>MVR/AVR/CABG</td>
<td>6–7</td>
<td>Al, NTG</td>
<td>3.7</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>M</td>
<td>Maze/MVR</td>
<td>∼3</td>
<td>...</td>
<td>4.8</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>M</td>
<td>Maze/MVR/CABG</td>
<td>∼5</td>
<td>Al, DIG</td>
<td>5.8</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>M</td>
<td>Maze/MVR</td>
<td>3</td>
<td>BB, NTG</td>
<td>4.5</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
<td>F</td>
<td>Maze</td>
<td>5</td>
<td>CC, DIG</td>
<td>4.9</td>
</tr>
<tr>
<td>9</td>
<td>74</td>
<td>F</td>
<td>Maze/MVR</td>
<td>4</td>
<td>AM, BB</td>
<td>5.2</td>
</tr>
<tr>
<td>10</td>
<td>52</td>
<td>M</td>
<td>Maze</td>
<td>10–15</td>
<td>AM, BB</td>
<td>4.3</td>
</tr>
<tr>
<td>11</td>
<td>66</td>
<td>F</td>
<td>Maze/MVR/CABG</td>
<td>4</td>
<td>Al, CC, DIG</td>
<td>6.6</td>
</tr>
</tbody>
</table>

MVR indicates mitral valve repair/replacement; ALB, albuterol. Other abbreviations are the same as in Table 1. In addition to the cardiovascular drugs listed, all of the chronic AF patients were on Coumadin therapy for anticoagulation.
postoperative AF. Half (19/38) of the surgical patients experienced postoperative AF. Figure 6A shows that there was no significant difference in either myocyte capacitance or the age between the patient groups, separated by postoperative AF occurrence. Figure 6B shows the mean±SEM current–voltage relations for the patients who experienced postoperative AF (●) versus those that did not (□). There was no difference in the voltage dependence of $I_{Ca}$ between groups, but the current density was significantly lower ($P<0.01$) in those patients who did not experience postoperative AF (peak $I_{Ca} = -5.96±0.6$ pA/pF, n=37) versus those who did ($-12.6±2.1$ pA/pF, n=35).

Figure 6C plots the peak $I_{Ca}$ density values of each myocyte, with symbols indicating the presence (●) or absence (□) of postoperative AF. Although there was a great deal of overlap at low $I_{Ca}$ densities, the myocytes with the greatest $I_{Ca}$ were isolated from patients who experienced postoperative AF. To account for the fact that different numbers of myocytes were studied per patient, we further analyzed the data by comparing the mean $I_{Ca}$ densities for each patient. Figure 6D shows that analysis of the data by patient means yielded the same result. The mean $I_{Ca}$ of the patients who did not experience postoperative AF ($-6.12±0.9$ pA/pF, n=19) was significantly lower compared with patients who did ($-10.3±1.9$ pA/pF, n=19; $P<0.05$).

**Discussion**

The present study demonstrates that atrial myocytes isolated from chronic AF patients have a significantly lower $I_{Ca}$ density than myocytes isolated from patients in normal sinus rhythm (Figure 2). The mean reduction in peak $I_{Ca}$ ($-3.35$ versus $-9.13$ pA/pF) was $63\%$. This is similar to the reduction that we previously detected in the transient outward $K^{+}$ current ($60\%$) and somewhat greater than the reduction in the sustained outward $K^{+}$ current ($50\%$) in myocytes from the same patient populations. Figure 2 shows that, although the $I_{Ca}$ density was reduced, there was no change in steady-state inactivation of $I_{Ca}$.
the voltage dependence of activation or steady-state inactivation of $I_{Ca}$ in the myocytes isolated from chronic AF patients. We previously showed that the reduction in outward $K^+$ current density was present only in those patients in whom AF was persistent. Patients with paroxysmal AF or dilated cardiomyopathy had normal outward $K^+$ current densities. In the present study, Figure 3 demonstrates that, although $I_{Ca}$ was consistently low in chronic AF patients, there was a significant overlap with many of the patients in normal sinus rhythm who also had low $I_{Ca}$ densities. Thus, whereas a low $I_{Ca}$ density is characteristic of myocytes from patients with chronic fibrillation, it is possible for patients to have myocytes with low $I_{Ca}$ density in the absence of AF.

Our results are consistent with the observation of Le Grand et al., who demonstrated a significant reduction in inward $Ca^{2+}$ and outward $K^+$ current densities in the myocytes of patients with dilated (but not necessarily fibrillating) atria. The presence of very large myocytes in the AF patient population (Figure 3A or 3B) is consistent with the presence of atrial dilation. However, we clearly demonstrate that the reduction in $I_{Ca}$ density is not solely due to a shift in myocyte size (Figure 3C). Both the $I_{Ca}$ amplitudes and current densities were reduced in the chronic AF patients, regardless of myocyte size.

Most of the chronic AF patients in the present study were undergoing mitral valve repair. Mitral regurgitation increases...
left atrial pressure and can directly cause significant left atrial dilation, in the absence of AF. However, the changes in İCa that we detected are not solely due to atrial dilation as a result of valvular disease. Two of the chronic AF patients (8 and 10) had no underlying valvular disease. The left atria of these patients were only modestly dilated (4.9 and 4.3 cm; normal left atrial dimension is 2 to 4 cm), and the mean İCa density of these patients (−2.9 pA/pF and −3.3 pA/pF) was indistinguishable from that of those AF patients with valvarul heart disease. Thus, it is likely that both atrial dilation and AF have a similar effect on atrial İCa.

Whereas heart failure is characterized by diminished adrenergic responsiveness, the present study shows that chronic AF does not diminish the İCa response to a maximal β-adrenergic stimulus. As shown in Figure 4, the response to maximal β-adrenergic stimulation was somewhat enhanced in the myocytes from the chronic AF patients. Neither the mechanistic basis for this response nor its significance is clear at this time. One might speculate that a greater fraction of the Ca2+ channels in the atrial myocytes from the chronic AF patients may be unavailable under basal conditions but can be recruited in the presence of adrenergic stimulation (perhaps as a result of altered phosphorylation status of the L-type Ca2+ channels). In any case, this result demonstrates that chronic AF does not result in a functional downregulation of all membrane proteins or signal transduction pathways.

In 1976, Hordof et al2 demonstrated that the plateau of action potentials recorded from atrial tissue of normal patients, but not those with AF, was attenuated in response to verapamil. Boutjdir et al4 demonstrated that action potentials recorded from atrial tissue isolated from patients with chronic AF had a shorter duration (APD90) and refractory period than tissue isolated from patients in normal sinus rhythm. The mechanisms responsible for these changes were not identified.

In rapidly paced canine atria, a significant reduction in the density of İCa has been reported, similarly resulting in an abbreviated action potential and decreased accommodation to changes in rate.3 In that study, superfusion of control myocytes with nifedipine (10 μmol/L) largely mimicked the changes observed after rapid atrial pacing. We have shown that nifedipine has the same effect on normal human atrial action potentials (Figure 5A through 5C) and that similar reductions in action potential duration and rate-dependent modulation of duration occur in atrial myocytes isolated from patients with chronic AF (Figure 5D through 5F). Our action potential recordings (Figure 5) are qualitatively similar to those recorded by Hordof et al2 and Boutjdir el al4 from intact, excised atrial tissue. Thus, in combination with the finding of decreased İCa density in the atrial myocytes from chronic AF patients, our study supports the evolving concept that İCa is a critical component of the normal cycle length–dependent modulation of atrial action potential duration.16,17

**Time Course of Human Atrial Electrophysiological Remodeling**

It is now evident that AF causes electrophysiological remodeling of the atria. Studies have demonstrated that these changes are rapid and are at least initially reversible.18 In addition to electrophysiological remodeling, there is also evidence for structural remodeling of the atria after prolonged periods of AF.19 In humans, structural changes may be due to both the underlying cardiac disease (eg, valvular problems, atherosclerosis, or cardiomyopathy) and the direct effects of the fibrillatory rhythm. Patients in the present study had AF for a long time, with a minimum duration of 3 years (Table 2). Given the duration of AF in the patients in the present study, no information about the time course of changes in İCa can be determined. Studies based on animal experiments in either fibrillating goats2,20 or rapidly paced canine atria3 suggest that significant electrophysiological remodeling can occur within a week of high-rate atrial activity.

Two recent biochemical studies on tissue isolated from patients with chronic AF both show that significant down-regulation of mRNA levels for the L-type Ca2+ channel was detectable after only 6 months of persistent AF.11,21 Evidence from both an animal model of AF10 and patients undergoing Maze surgery12 suggests that mRNA changes result in reduced expression of the α1 subunit of the L-type Ca2+ channel. Our study complements these results and directly demonstrates that there is a significant (63%) reduction in the density of İCa in atrial myocytes isolated from patients with chronic AF. This decrement in İCa is likely to contribute to the changes in action potential morphology and to the loss of adaptation of action potential duration as a function of activation rate that are characteristic of recordings from chronic AF patients and from those patients vulnerable to arrhythmia induction.

**Structural Remodeling**

In addition to electrophysiological remodeling, chronic AF is also associated with structural changes in the atria. In atrial tissue from many of the patients studied, there was a significant accumulation of fatty deposits in the atria and a loss of the trabeculation of the left atria. These changes may have a significant effect on the pathways of atrial excitation and the tendency to maintain AF. We have not yet begun to quantitatively assess the structural remodeling, but we note that it was quite variable from patient to patient. It could not be easily correlated with the duration of chronic AF, the age of the patient, or the presence of valvular regurgitation. Thus, regardless of the time course of the electrophysiological remodeling, it is likely that once a patient is restored to sinus rhythm, the time required for structural remodeling of the atria (if it is even possible) will vary greatly and will likely be much slower than the electrophysiological remodeling of the individual atrial myocytes. These considerations reinforce the concept that early intervention in terminating AF may be desirable.

**Postoperative AF**

AF in the postoperative period is a common complication of cardiac surgery, occurring in 30% to 60% of all patients. Postoperative AF increases the risk of embolic events and stroke to the patient. It also increases the length of stay and, thus, the costs associated with being in the hospital.22 The causes of postoperative AF are not well understood and may be mechanistically different from nonsurgically induced AF.
reflecting, in part, the response to a variety of intraoperative and/or postoperative factors associated with the overall surgical trauma. In the present study, the incidence of postoperative AF was 50%. When comparing those patients in the present study who did and who did not experience postoperative AF, we found that myocytes in both groups were of similar size and that the patients who experienced postoperative AF tended to be older but were not significantly different in age (Figure 6A). We initially anticipated that patients with a lower $I_{Ca}$ would be more likely to sustain reentrant activity, owing to a predicted shorter wavelength. On the contrary, our results revealed (Figure 6B) a positive correlation between $I_{Ca}$ measured at the time of surgery and the occurrence of postoperative AF. As demonstrated in Figure 6C, the myocytes with the greatest $I_{Ca}$ were all from patients who experienced postoperative AF. By averaging the mean $I_{Ca}$ densities for all myocytes from each patient (Figure 6D), we reduced the possibility that sampling bias from a few patients shifted the means artificially. This analysis yielded the same result. In view of the significant overlap in the $Ca^{2+}$ current density data for most patients, we suggest that the preoperative $Ca^{2+}$ current density is an additional factor (but clearly not the only factor) that modulates the propensity of the patient to develop postoperative AF after cardiac surgery.

It has recently been demonstrated that administration of calcium channel blockers before the initiation of AF can blunt or prevent the electrophysiological remodeling that accompanies AF. Calcium overload has also been suggested to be an important factor in the initiation of arrhythmias. The postoperative setting is one of high sympathetic tone. As calcium influx through L-type Ca$^{2+}$ channels plays a crucial role in atrial excitation-contraction coupling. Atrial mechanical function, as well as the amplitude of the cytosolic calcium transient, is also impaired in a canine model of AF. We suggest that the electrophysiological remodeling that develops during chronic AF, resulting in significantly decreased $I_{Ca}$, is likely to contribute to the impairment of atrial mechanical function.

In contrast to the effects of chronic AF, some surgical patients in normal sinus rhythm with greater $I_{Ca}$ may be predisposed to the development of postoperative AF. We suggest that calcium overload may contribute to the arrhythmogenesis in this setting, in response to the high sympathetic tone in the postoperative setting. For patients who have good cardiac function, prophylactic maintenance of these patients with beta-blocker therapy during the postoperative period would thus be logical and unlikely to present significant risk. In contrast, treatment of these patients with digoxin (for ventricular rate control after AF has appeared) seems counterintuitive, because it would further exacerbate the calcium overload of the atria. A combination of beta-blockers and/or calcium channel blockers (to slow the ventricular rate) would be a more logical treatment.

Summary/Implications

Calcium influx via L-type Ca$^{2+}$ channels plays a crucial role in atrial excitation-contraction coupling. Atrial mechanical function is impaired in chronic AF patients and returns slowly (and only partially) after the Maze procedure (as assessed with echocardiography). Atrial mechanical function, as well as the amplitude of the cytosolic calcium transient, is also impaired in a canine model of AF. We suggest that the electrophysiological remodeling that develops during chronic AF, resulting in significantly decreased $I_{Ca}$, is likely to contribute to the impairment of atrial mechanical function.

In contrast to the effects of chronic AF, some surgical patients in normal sinus rhythm with greater $I_{Ca}$ may be predisposed to the development of postoperative AF. We suggest that calcium overload may contribute to the arrhythmogenesis in this setting, in response to the high sympathetic tone in the postoperative setting. For patients who have good cardiac function, prophylactic maintenance of these patients with beta-blocker therapy during the postoperative period would thus be logical and unlikely to present significant risk. In contrast, treatment of these patients with digoxin (for ventricular rate control after AF has appeared) seems counterintuitive, because it would further exacerbate the calcium overload of the atria. A combination of beta-blockers and/or calcium channel blockers (to slow the ventricular rate) would be a more logical treatment.

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References


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David R. Van Wagoner, Amber L. Pond, Michelle Lamorgese, Sandra S. Rossie, Patrick M. McCarthy and Jeanne M. Nerbonne

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