Electrophysiological Characteristics of the Human Atria After Cardioversion of Persistent Atrial Fibrillation

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Background—In animal models, induced atrial fibrillation shortens the atrial effective refractory period (ERP) and reverses its physiological adaptation to rate. It is not clear whether this process, known as “electrical remodeling,” occurs in humans.

Methods and Results—We determined the ERPs, at 5 pacing cycle lengths (300 to 700 ms) and in 5 right atrial sites, after internal cardioversion of chronic atrial fibrillation in 25 patients (14 in pharmacological washout and 11 on amiodarone). The ERPs were 195.5 ± 18.8 ms in the washout and 206.3 ± 17.9 ms in the amiodarone patients (P < 0.0001). ERPs were closely correlated with the stimulation rates (r = 0.95 in the washout and r = 0.94 in the amiodarone group), and slope values indicating a normal (≥0.07) or nearly normal (0.05 to 0.06) adaptation of ERP to rate were found in 77% of the 84 paced sites. The mean ERP was shorter in the lateral wall (198.1 ± 17.9 ms) than in the atrial roof (203.3 ± 21.5 ms) and in the septum (210.5 ± 20.0 ms) (P < 0.03). After 4 weeks of sinus rhythm, the mean ERP, determined again in 8 patients (4 in wash-out and 4 on amiodarone), was significantly increased compared with the basal study (221.4 ± 21.4 versus 197.8 ± 18.3 ms, P < 0.0001).

Conclusions—After cardioversion of chronic atrial fibrillation, (1) atrial ERP adaptation to rate was normal or nearly normal in the majority of the cases, (2) a significant dispersion of refractoriness between different right atrial sites was present, and (3) ERPs were significantly increased after 4 weeks of sinus rhythm in both washout and amiodarone patients. (Circulation. 1998;98:2860-2865.)

Key Words: fibrillation n remodeling n electrophysiology n atrium

Atrial fibrillation (AF) is maintained by multiple wandering wavelets continuously reentering themselves.1-3 The number of the wavelets is related to the atrial mass and to the wavelength (product of refractoriness and conduction velocity) of the reentrant circuits.4,5 Short wavelengths allow the simultaneous presence of a greater number of wavelets, whereas long wavelengths reduce their number, making the occurrence of simultaneous extinction of all the wavelets and the termination of the arrhythmia more likely.4 Therefore, the 2 components of the wavelength, conduction velocity and atrial refractoriness, are basic determinants of the AF onset and perpetuation. A third important factor favoring the onset of the arrhythmia is dispersion of refractoriness. In fact, after a premature impulse, it increases the likelihood of local unidirectional block, one of the prerequisites of a reentrant circuit.3

Recently, Wijffels8 demonstrated in healthy goats that the artificial maintenance of AF by rapid atrial pacing induced a progressive shortening of the atrial effective refractory period (ERP). Moreover, the rate-related shortening of ERP was inverted, resulting in shorter refractoriness at lower rates. The loss of the normal increase in refractoriness with a decrease in rate could be another important factor favoring AF. In fact, it might facilitate the induction of the arrhythmia by a premature atrial beat during normal sinus rhythm. These changes in the refractoriness behavior have been called “electrical remodeling” and constitute the experimental basis of the concept that AF tends to perpetuate itself: “AF begets AF.”

Nevertheless, the findings observed in AF induced in healthy goats are not necessarily applicable to the patients with the same spontaneous arrhythmia, even though shortening of the atrial ERPs after as little as 7 or 8 minutes of pacing-induced AF9 and short ERPs after cardioversion of chronic lone AF10 have been demonstrated in humans. Moreover, it is not known whether other peculiar electrophysiological features, such as an abnormal response of atrial refractoriness to abrupt cycle length changes, are present after cardioversion of clinical persistent AF.

The present study was conducted in patients with spontaneous chronic AF immediately after internal electrical cardioversion and was designed to assess the following:

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the atrial ERPs immediately after cardioversion and their behavior with time, the relation between stimulation rate and ERPs, the dispersion of refractoriness in the right atrium, the refractoriness response to long-short and short-long cycles, and the effects of amiodarone on the above parameters.

Methods

Patient Selection
The study was carried out in 25 consecutive patients with chronic AF (duration between 30 days and 4 years) 5 minutes after low-energy internal cardioversion. The study was approved by our Institutional Ethical Committee, and all the patients gave written informed consent.

The diagnosis of AF was based on the surface ECG, with the following criteria: presence of fluctuation of the baseline without regular P or F waves, with totally irregular RR intervals. These criteria had to be validated by endocardial recordings showing irregular atrial activation not separated by an isoelectric line or discrete atrial complexes separated by an isoelectric line but with irregular atrial intervals (FF). Moreover, no periodic pattern of the FF intervals could be present.11,12

Thyroid dysfunction had been ruled out in all patients. Eleven patients were on amiodarone treatment; the remaining 14 were in therapeutic washout (no antiarrhythmic drugs, verapamil, or digoxin included). As a rule, the patients in washout were treated with intravenous propafenone (2 mg/kg) after the completion of the protocol, followed by oral administration of the drug (600 to 750 mg/d).

Electrophysiological Study
Two catheters were used for each patient; they were introduced in the same sheaths as used for the leads necessary for internal cardioversion. A standard quadripolar lead with 2-mm spacing (Bard-USCI Inc) was positioned in the right atrium, allowing simultaneous recording of bipolar electrograms from the distal and proximal pairs. A second catheter was also positioned in the right atrium for monophasic action potential recording. This lead (Franz catheter, EP Technologies) was preferred for its low stimulation threshold.

A value of $P<0.05$ was considered statistically significant.

Statistical Analysis
For each paced site, the linear correlation between the ERPs and the corresponding pacing rates was calculated by the single linear regression analysis. The presence of normal or abnormal refractoriness adaptation to rate and its degree were also established by evaluation of the slope values. According to the slope figures, the adaptation of the ERP to rate was considered absent when the slope value was zero and inverted if its value was negative. For positive values between 0.01 and 0.04, the adaptation was considered poor; between 0.05 and 0.06, it was considered nearly normal; and for values $\geq0.07$, it was classified as normal.

Data are presented as mean±SD. Differences in continuous variables were analyzed by paired or unpaired Student's $t$ test or ANOVA as appropriate, and comparisons between groups were performed by multiple Bonferroni test. Differences in categorical variables were analyzed by $\chi^2$ test, with Yates' correction if needed. A value of $P<0.05$ was considered statistically significant.

Results

Patients and Paced Sites
Seventeen patients were men and 8 women, with a mean age of 61.6±8.8 years; AF duration was $\geq30$ days in all the patients (mean, 220.8±366.1 days; median, 90.0 days; range, 30 to 1440 days). Ten patients had a history of paroxysmal AF in the preceding years. The mean left atrial size was 46.0±5.7 mm (median, 45.0 mm; range, 38 to 59 mm). The underlying heart diseases were as follows: valvular heart disease (4 patients), hypertension (8), dilated cardiomyopathy (3), hypertrophic cardiomyopathy (1), and coronary heart disease (5). Four patients had lone AF. In 7 of the 25 patients, the study was stopped because of AF induction during the first or the second stimulation sequence in the first paced site. Six of these patients were in washout, and 1 was on amiodarone. Therefore, the stimulation protocol was carried out in 18 patients, 10 on amiodarone and 8 in washout. It was performed in all the 5 sites in 14 patients (7 in washout and 7 on amiodarone), in 4 sites in 1 patient (on amiodarone), and in 3 sites in 3 patients (1 in washout and 2 on amiodarone), for a total of 84 sites. In 2 patients (1 in washout and 1 on amiodarone), the sequence at 700-ms cycle length was not performed because of the higher sinus rate.

In 2 of the 10 patients who underwent the second electrophysiological study 4 weeks after the first one (1 in washout and 1 on amiodarone), AF was reinduced during determina-
tion of refractoriness at the first selected site during the first or second cycle length. Therefore, the second electrophysiological study was carried out in 8 patients (4 in washout and 4 on amiodarone).

The pertinent clinical and electrophysiological features of the patients initially recruited, both those who underwent the full set of initial tests and those who underwent the second study, are reported in Table 1. Table 2 shows the sites at which the stimulation was performed in both the initial and the second study.

### Adaptation of ERPs to Rate

Taking into account all the paced sites, the mean ERPs at the different stimulation cycle lengths in both groups of washout and amiodarone patients are reported in Table 3. At all stimulation cycles, the ERPs were significantly shorter in the washout than the amiodarone patients.

As graphically shown in Figure 1, there was a linear correlation between the mean atrial ERPs and the stimulation rate \( r = 0.95 \) in the washout group and \( r = 0.94 \) in the amiodarone group. The mean slope value was 0.07 ± 0.03 in the washout group and 0.07 ± 0.04 in the amiodarone group.

Considering the individual stimulation sites, slope values ≥0.07 were present in 47 sites (60%), slope values between 0.05 and 0.06 in 18 sites (21%), slope values between 0.01 and 0.04 in 16 sites (19%), and a slope value of 0 in 1 site (1%). No negative slope values were found in any site. Therefore, a normal or nearly normal adaptation to the rate was present in 65 sites (77%): 31 (82%) in the washout and 34 (74%) in the amiodarone patients.

### Dispersion of Refractoriness

As illustrated in Figure 2, the ERPs were significantly shorter in the lateral right atrial sites (198.1 ± 17.9 ms) than in the atrial roof (203.3 ± 21.5 ms) and in the septum (210.5 ± 20.0 ms) \( (P < 0.03) \). These results demonstrate the presence of a significant dispersion of refractoriness within the right atrium after cardioversion of chronic AF.

### Effect of the Long-Short and Short-Long Sequences

The determination of refractoriness after a long-short and a short-long sequence was performed in 14 patients, 7 in washout and 7 on amiodarone. The results are shown in Table 4.

The mean ERP after the long-short sequence (basic cycle length, 600 ms, followed by a beat at 300 ms) was significantly shorter than the ERP found during constant pacing at 300 ms \( (170.9 ± 12.1 \text{ ms} \text{ versus } 181.8 ± 17.0 \text{ ms}, P < 0.001) \) (Figure 3), implying an overshoot of the adaptation of refractoriness to the preceding premature beat. The overshoot was not bidirectional, that is, no difference was found between the atrial ERP during the short-long sequence (basic cycle length, 300 ms, followed by a beat at 600 ms) and the ERP during constant pacing at 600 ms \( (211.6 ± 23.3 \text{ ms} \text{ versus } 204.2 ± 19.1 \text{ ms}, P = \text{NS}) \) (Figure 3).

### Changes of Refractoriness With Time

In the 8 patients who completed the second electrophysiological study (4 in washout and 4 on amiodarone), the mean atrial ERPs were found to be significantly increased at all the basic stimulation cycles with respect to the basal study in both the washout and the amiodarone patients (Table 5). For each stimulation cycle length, the ERPs were shorter in washout than in amiodarone patients.

The adaptation of the refractoriness to the rate was found to be normal or nearly normal in both the washout and amiodarone groups and was similar to that observed immediately after cardioversion \( (r = 0.95 \text{ in the washout group and } r = 0.96 \text{ in the amiodarone group}) \). The mean slope values were 0.08 in the washout patients and 0.07 in the amiodarone patients.

### TABLE 2. No. of Sites at Which the Stimulation Protocol Was Performed in Washout and Amiodarone Patients

<table>
<thead>
<tr>
<th>Lateral</th>
<th>Washout</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Mid</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>High</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Roof</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Septum</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>46</td>
</tr>
</tbody>
</table>

### TABLE 1. Clinical Data of the Studied Patients

<table>
<thead>
<tr>
<th></th>
<th>Washout</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.6 ± 8.8</td>
<td>62.2 ± 9.1</td>
</tr>
<tr>
<td>Sex, M/F, n</td>
<td>17/8</td>
<td>13/5</td>
</tr>
<tr>
<td>AF duration, d</td>
<td>220.8 ± 366.1</td>
<td>231.1 ± 353.1</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>46.0 ± 5.7</td>
<td>45.8 ± 5.6</td>
</tr>
<tr>
<td>Washout, n</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Amiodarone, n</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

### TABLE 3. Refractory Periods (Mean ± SD of All Paced Sites) at Each Basic Cycle Length in Washout and Amiodarone Patients

<table>
<thead>
<tr>
<th>Basic Cycle Length</th>
<th>Washout</th>
<th>Amiodarone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>190.2 ± 14.6</td>
<td>192.3 ± 15.9</td>
<td>0.0006</td>
</tr>
<tr>
<td>400</td>
<td>190.8 ± 16.8</td>
<td>200.9 ± 15.8</td>
<td>0.006</td>
</tr>
<tr>
<td>500</td>
<td>197.5 ± 17.4</td>
<td>207.5 ± 16.2</td>
<td>0.007</td>
</tr>
<tr>
<td>600</td>
<td>203.0 ± 17.5</td>
<td>214.4 ± 17.0</td>
<td>0.003</td>
</tr>
<tr>
<td>700</td>
<td>207.4 ± 18.8</td>
<td>217.8 ± 16.5</td>
<td>0.01</td>
</tr>
<tr>
<td>All</td>
<td>195.5 ± 18.8</td>
<td>206.3 ± 17.9</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
The ERPs were still different in the various right atrial sites: 217.5±21.3 ms in the lateral wall, 226.3±20.1 ms in the roof, and 234.0±19.0 ms in the septum (P<0.003).

**Discussion**

Sinus rhythm can be restored by pharmacological or electrical cardioversion in the great majority of the patients with chronic AF, but frequently the arrhythmia recurs despite antiarrhythmic drug treatment. The recurrence rate is higher in patients with a longer duration of the arrhythmia, and the arrhythmia relapse usually occurs in the first days or weeks after cardioversion. These findings are in agreement with the concept of atrial "electrical remodeling" considered to be induced by sustained rapid rates, suggesting that some electrophysiological features found in patients with AF and favoring the arrhythmia recurrence could be the consequence, and not the cause, of the arrhythmia itself.

**Previous Studies on Atrial Electrophysiological Features Associated With AF**

In goats, the artificial maintenance of AF or longstanding high-rate atrial pacing was found to produce a marked shortening of refractoriness with a reversion of its physiological adaptation to rate. Shortening of the ERPs after 7 hours of constant atrial pacing was also demonstrated in dogs. In humans, a significant reduction in atrial refractoriness after several minutes of induced AF has been described, and after cardioversion of chronic lone AF, ERPs were shorter than in a control group of patients without atrial arrhythmias. Failure in the rate adaptation of the atrial ERP has been found in patients with either increased atrial vulnerability or atrial arrhythmias at Holter monitoring. Finally, shorter ERPs and a reverse adaptation to rate were found in the atrial appendages of patients with chronic AF and rheumatic heart disease undergoing corrective cardiac surgery.

Two other factors recognized as favoring the arrhythmia are dispersion of refractoriness and decreased conduction velocity. The first one does not appear to be the consequence of rapid atrial rates, but it seems to be related to local vagal influence, atrial fibrosis, and age. Conduction velocity also appears to be related to cellular fibrosis and uncoupling present in ill or aged atria, but it was prolonged even in healthy dogs with induced chronic AF. In goats, however, conduction velocity was not found to be affected by sustained rapid atrial rates.

**Atrial Refractoriness and Its Adaptation to Rate**

In our study, atrial ERPs were found to be shorter immediately after cardioversion than 4 weeks after sinus rhythm restoration. This is in agreement with the previous finding that long-lasting AF causes shortening of refractoriness. As expected, patients in washout had shorter ERPs than patients on amiodarone, both at baseline and 4 weeks later.

Contrary to what was previously reported in both animals and humans, we found a normal or nearly normal adaptation of the ERPs to the stimulation rate after cardioversion of persistent AF in the great majority of the right atrial sites of our patients. It can be argued that, in animal models, the pacing-induced AF may be an arrhythmia that is somehow different from the chronic AF in humans in terms of arrhythmia duration and presence of atrial disease. Moreover, species-specific differences in modulation of ion channel gene expression might play a role in determining a different behavior.

Other human studies have been conducted on patients who are different from ours. In fact, Attuel et al studied subjects with atrial vulnerability at electrophysiological study or with paroxysmal atrial tachyarrhythmias by Holter monitoring and not patients with chronic AF. Indeed, the results of Le Heuzey et al in an ex vivo study are only apparently different from ours. In fact, they did find a reverse rate-related adaptation of the refractoriness, but only for very long cycle lengths (from 1200 to 1600 ms). Until these very low rates, usually not achievable in the electrophysiological laboratory because of the higher sinus rate, the adaptation of refractoriness to rate was conserved. Our study does not exclude the possibility that at lower sinus rates, which may be present only in patients with sick sinus syndrome, a reverse adaptation to rate could be possible.

Our finding that a normal or nearly normal adaptation of ERPs to rate is present after cardioversion of chronic AF means that this is probably not a cause of maintenance of the arrhythmia or of the recurrence of arrhythmia after cardioversion in humans. Nevertheless, our data showing...
TABLE 4. Refractory Periods at Constant Pacing of 300 and 600 ms Compared With Long-Short (600 to 300 ms) and Short-Long (300 to 600) Sequences

<table>
<thead>
<tr>
<th>Paced Sites, n</th>
<th>Washout 31</th>
<th>Amiodarone 33</th>
<th>All 64</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>178.4±14.0</td>
<td>190.0±16.5</td>
<td>181.8±17.0</td>
</tr>
<tr>
<td>600 to 300</td>
<td>166.3±10.0</td>
<td>176.0±12.0</td>
<td>170.9±12.1</td>
</tr>
<tr>
<td>P</td>
<td>0.03</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>600</td>
<td>198.1±19.4</td>
<td>210.8±16.8</td>
<td>204.2±19.1</td>
</tr>
<tr>
<td>300 to 600</td>
<td>201.3±18.7</td>
<td>222.4±23.3</td>
<td>211.6±23.3</td>
</tr>
<tr>
<td>P</td>
<td>0.6</td>
<td>0.07</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Effect of Abrupt Cycle Length Changes on Refractoriness

In normal subjects, the ERP of atrial myocardium abruptly and appropriately adjusts to the duration of the last cycle, whereas adaptation of ventricular myocardium reflects the cumulative effect of the preceding cycles, and His-Purkinje refractoriness overshoots in the direction of the preceding cycle length change.\(^{31,32}\) The behavior of the response of atrial refractoriness to an abrupt change of cycle length in patients with persistent AF after cardioversion is unknown at this time, although an abnormal response could affect the likelihood of AF relapse.

In our study, atrial refractoriness showed an abnormal overshoot in adaptation after a long-short sequence. This phenomenon may have clinical relevance, because it could contribute to the frequent recurrence of the arrhythmia in the first days after cardioversion. In fact, a marked reduction of atrial refractoriness, and thus a shortening of the cycle length caused by a premature beat could favor the reinduction of AF by a second short-coupled premature beat.

Conclusions

Our study, conducted in patients with spontaneous chronic AF, confirms that after cardioversion of the arrhythmia, atrial ERPs are short and tend to increase with time. Moreover, a significant dispersion of refractoriness was present in the right atrium, as well as an abnormal response of the ERPs to an abrupt shortening of the stimulation cycle. All these findings can concur to explain the tendency of AF to be sustained and to recur. However, we did not find failure of the adaptation of refractoriness to rate. This phenomenon, observed experimentally in animals, thus cannot be considered a cause of the early recurrence of the arrhythmia after cardioversion in humans. This also means that caution has to
be exerted in automatically extending to humans the results achieved in animal models.

References

1. Moe GK. On the multiple wavelet hypothesis of AF. Arch Int Pharmacodyn Ther. 1962;140:183–188.

TABLE 5. Difference Between Basal and Follow-Up Refractory Periods at All Basic Stimulation Cycles, in Both the Washout and the Amiodarone Groups

<table>
<thead>
<tr>
<th>Basic Cycle Length, ms</th>
<th>Washout</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>180.0±15.0</td>
<td>180.0±11.0</td>
</tr>
<tr>
<td>400</td>
<td>198.6±16.2</td>
<td>198.6±12.3</td>
</tr>
<tr>
<td>500</td>
<td>201.7±17.6</td>
<td>201.7±13.5</td>
</tr>
<tr>
<td>600</td>
<td>201.7±16.0</td>
<td>201.7±13.5</td>
</tr>
<tr>
<td>700</td>
<td>201.7±16.0</td>
<td>201.7±13.5</td>
</tr>
</tbody>
</table>

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