Are Electrophysiological Changes Induced by Longer Lasting Atrial Fibrillation Reversible?
Observations Using the Atrial Defibrillator

Luz-Maria Rodriguez, MD; Carl Timmermans, MD; Hein J.J. Wellens, MD

Background—Studies in animal hearts have shown shortening of the atrial effective refractory period (AERP) and loss of the relation between the AERP and heart rate after prolonged periods of atrial fibrillation (AF). The purposes of this study were (1) to evaluate atrial electrophysiology after a long period of sinus rhythm in patients who had longer lasting recurrent AF that was successfully treated with the Metrix Atrioverter and (2) to analyze the effect of prompt cardioversion on subsequent AF episodes and the duration of sinus rhythm.

Methods and Results—Four patients with recurrent AF (duration, 3 to 21 years; mean±SD, 13±7.6 years) were studied after the implantation of an Atrioverter. The Atrioverter stores and analyzes 3 minutes of cardiac rhythm every hour. Before implantation, AERP was measured. During a mean follow-up of 14 months, 52 spontaneous (39 treated and 18 nontreated) AF episodes occurred while the patients were on antiarrhythmic drugs. All patients were electrophysiologically studied after they had been in sinus rhythm for at least 1000 hours (range, 1052 to 2675 hours). Before Atrioverter implantation, AF was induced by 1 atrial premature beat in 3 patients and not induced in the remaining patient. After a long period in sinus rhythm (>1000 hours), AF could be induced in the same 3 patients in the same way as before implantation. In the patient in whom no AF was induced, right AERP values measured using the single extrastimulus technique at 3 pacing cycle lengths (600, 500, and 430 ms) were similar to those before implantation.

Conclusions—AF was still inducible by a single atrial premature beat after long episodes of sinus rhythm in 3 of 4 patients with previously longer lasting AF. In the patient in whom no AF was induced, AERP behaved like it did before implantation. In these patients with longer lasting recurrent AF, no return to “normal” atrial electrophysiology could be demonstrated. (Circulation. 1999;100:113-116.)

Key Words: atrium • fibrillation • remodeling • defibrillation

Studies in the goat showed shortening of the atrial effective refractory period (AERP) and loss of the relation between the AERP duration and heart rate after prolonged periods of atrial fibrillation (AF) (remodeling). Furthermore, AF was more difficult to reinduce as time after conversion of an AF episode increased. Those experiments suggested that the findings on atrial electrophysiology after long periods of AF were the result rather than the cause of AF. They also argued for prompt termination of AF using conventional or new modalities to reverse the electrophysiological changes favoring the development of long-term AF. The purposes of this study were (1) to evaluate the electrophysiological properties of the atrium after a long period of sinus rhythm in patients who previously had long-lasting recurrent AF that was promptly and successfully treated with the Metrix Atrioverter and (2) to analyze the effect of prompt cardioversion on subsequent AF episodes and the duration of sinus rhythm.

Methods

Patients

Until May of 1998, 13 patients with recurrent, drug-refractory AF received the Metrix Atrioverter (In Control Inc.) at our institution. The 4 patients with the longest follow-up are the subject of this study. Their clinical characteristics are given in the Table. The mean duration of the arrhythmia before Atrioverter implantation was 13±7.6 years.

Electrophysiological Study

All patients underwent internal atrial defibrillation before implantation. This technique has been described elsewhere. Except for amiodarone, antiarrhythmic drugs (AAD) were discontinued for at least 5 half-lives before the electrophysiologic study. After 10 minutes of stable sinus rhythm, electrophysiological examination was performed. In addition, a quadripolar catheter was positioned in the high right atrium to measure the AERP. Electrodes 1 and 2 were used for pacing and electrodes 3 and 4 to record atrial activity. The AERP was defined as the longest S1-S2 coupling interval failing atrial capture. The mean atrial pacing threshold was 1±0.3 mA. Pacing was performed at twice threshold. After a
Clinical Characteristics of the Patients Studied

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Before LA size, mm</th>
<th>After LA size, mm</th>
<th>Failed AAD, No. (median)</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>51</td>
<td>47</td>
<td>41</td>
<td>4</td>
<td>Lone</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>65</td>
<td>46</td>
<td>45</td>
<td>3</td>
<td>Lone</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>65</td>
<td>58</td>
<td>56</td>
<td>4</td>
<td>CAD</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>66</td>
<td>53</td>
<td>46</td>
<td>4</td>
<td>Lone</td>
</tr>
</tbody>
</table>

After indicates after implant; before, before implant; CAD, coronary artery disease; F, female; LA, left atrium; and M, male.

Results

Atrial Fibrillation Episodes Before Implantation
Patient 1 had 1 AF episode every month that lasted from hours to 5 days. During the last 2 years, these episodes required external cardioversion to achieve sinus rhythm. Patient 2 experienced daily AF episodes lasting from minutes to hours. Patient 3 had, in the last 2 years, 1 AF episode per month lasting from hours to 1 week. Conversion to sinus rhythm could only be obtained with external cardioversion. Finally, patient 4 experienced 1 AF episode every 3 months. These episodes lasted 3 days and required external cardioversion.

Electrophysiologic Findings Before Implantation
Before implantation, sustained (>30 minutes) AF was easily induced with 1 atrial premature beat (APB) in 3 patients. In patient 1, AF was induced with a drive cycle length of 600 ms and S1-S2 of 260 ms. In patient 2, AF was induced with a drive cycle length of 600 ms and S1-S2 of 280 ms, and in patient 4, with a drive cycle length of 500 ms and a S1-S2 of 280 ms. In patient 3, AF could not be induced using 3 different pacing cycle lengths and up to 2 atrial extrastimuli. The AERPs measured in the high right atrium with a drive cycle length of 600, 500, and 430 ms were 200, 220, and 200 ms, respectively.

Spontaneous AF Episodes After Implantation
In a follow-up period of 597 days, patient 1 had 7 treated and 2 nontreated (self-terminating) spontaneous episodes of AF. The mean duration of the treated episodes was 13.06 ± 8.36 hours (range, 7 to 33 hours), and the durations of the 2 nontreated episodes were 7 and 8 hours, respectively. Patient 2 had 14 treated and 10 nontreated episodes of AF in a follow-up of 365 days. The mean duration of the treated episodes was 5.53 ± 3.38 hours (range, 3.3 to 10 hours) and of the nontreated episodes, 5.30 ± 3.77 hours (0.5 to 14.3 hours). Patient 3 had 15 treated and 6 nontreated episodes of AF in a period of 401 days. The mean duration of the treated episodes was 10.39 ± 4.61 hours (range, 4 to 17.3 hours). All 6 nontreated AF episodes lasted less than 1 hour. Finally, patient 4 had only 3 AF episodes (all treated) within a period of 288 days. The mean duration of these episodes was 31.57 ± 31.0 hours (range, 10.5 to 107 hours). The reason why this patient had longer durations of AF episodes than the other 3 patients was because the patient was less symptomatic.

During the course of this study, the AAD regimen was unchanged in patients 1, 3, and 4, whereas in patient 2, sotalol was added to flecainide. Thus, the current medication consisted of amiodarone in patient 1, sotalol and flecainide in patient 2, flecainide and metoprolol in patient 3, and amiodarone in patient 4.

Electrophysiologic Findings After a Long Period of Sinus Rhythm
Sustained (>30 minutes) AF was induced in patient 1 after 1052 hours (43.8 days) of sinus rhythm. AF was induced at a drive cycle length of 500 ms and a S1-S2 of 300 ms. This episode was terminated with a 3-J shock from the Atrioverter. In patient 2, sustained AF was induced at a drive cycle length of 600 ms and a S1-S2 of 230 ms after being in sinus rhythm for a period of 2675 hours (111.46 days). This episode was converted to sinus rhythm with 150 mg of flecainide intravenously. In patient 3, AF could not be induced by atrial pacing using 3 different pacing cycle lengths and up to 2 APBs after a period of sinus rhythm of 1075 hours (44.79 days). The AERP values measured in the high right atrium at drive cycle lengths of 600, 500, and 430 ms were 250, 240, and 250 ms, respectively. Finally, in patient 4, AF was induced at a drive cycle length of 500 ms and a single APB of 240 ms after 2374 hours (98.9 days) of sinus rhythm. In this patient, stable sinus rhythm was obtained after 2 Atrioverter shocks of 6 J and the intravenous administration of 150 mg of flecainide.

Effect of Internal Atrial Defibrillation on AF and Sinus Rhythm Duration
The effect of repeated internal atrial defibrillation on the duration of AF and sinus rhythm duration is shown in the Figure. Only in patient 2 did the duration of the AF episodes seem to shorten and the duration of sinus rhythm to prolong as the time from implantation increased. The duration of sinus rhythm started to prolong 120 days after implantation. In the remaining 3 patients, the effect of repeated cardioversion on the prolongation of the duration of sinus rhythm and the shortening of the duration of AF episodes did not (yet?) occur.

Discussion
To our knowledge, this is the first study prospectively reporting on atrial electrophysiology after a long period of
sinus rhythm (>40 days) in patients with recurrent AF treated with the Atrioverter. It shows that in patients with recurrent AF, despite the fact that the atria have been in sinus rhythm for a long period, sustained AF (>30 minutes) was easily induced with 1 APB in 3 patients. In the remaining patient in whom no AF could be induced, the lack of rate-dependent behavior of the AERP remained unchanged. Repetitive internal atrial defibrillation resulted in shortening of the duration of the AF episodes and prolongation of the duration of sinus rhythm in only 1 patient. In goats with induced long-term AF, changes in atrial electrophysiology completely reverted after 1 week of sinus rhythm. Moreover, the inducibility of AF became more difficult after 1 week of sinus rhythm.1

In induced AF episodes in the human heart,5,6 without documentation of spontaneous AF, it was shown that the AERP after AF returned to preAF measurements after a mean of 85 or 136 minutes. Furthermore, in those studies, induction of a second AF episode became more difficult as time elapsed from spontaneous conversion; it was 0% at 10 minutes.5

At the time of this second electrophysiologic study of our patients on AADs, AF was still inducible in 3 patients. In the patient in whom AF was not inducible, the AERP had increased slightly.

Our study does not question the value of the implantable atrial defibrillator to rapidly convert atrial fibrillation to sinus rhythm, but the observations in our 4 patients with longer lasting recurrent AF showed that atrial electrophysiology did not return to normal. If the nontreated episodes (>5 hours) were responsible for this unchanged atrial electrophysiology, it would imply that all shorter episodes need to be treated promptly to obtain complete restoration of atrial electrophysiology. It may be more likely, however, that after a long period of AF recurrences, morphological, genetic, and electrophysiologic changes occur that prevent atrial electrophysiology from returning to normal. It is clear that the type of AF in our patients differed from the first episode of longer lasting AF studied in goats.1 The possibility of reversing the atrial electrophysiologic changes in patients after the conversion of their first few episodes of AF must be investigated. More information is needed about the role of the number and

Graphs for each patient depicting the day and the duration of AF episodes (○, corresponding to the vertical bar on the right side of the figure) and the duration of sinus rhythm (black bars, corresponding to the vertical bar on the left side of the figure) from the day of implantation (day 0) until the end of the observation. The second electrophysiologic study (PES) was performed after the last period of sinus rhythm.
duration of AF episodes on the reversibility of changes in atrial electrophysiology.

Limitations of the Study
The small number of patients included in our study is a limitation. Furthermore, the Atrioverter was programmed to detect AF every 60 minutes. Some short-lasting AF episodes occurring between 2 scanning intervals were perhaps not detected by the device.

Conclusion
In 4 patients with a long-standing history of recurrent AF who were treated with the implantable Atrioverter, AF was easily reinduced by a single APB after a long episode of sinus rhythm in 3 patients. In the patient in whom AF was not induced, the AERP had not changed compared with values before Atrioverter implantation. Therefore, in these patients, no return to “normal” atrial electrophysiology could be demonstrated.

References
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