Spontaneous Episodes of Atrial Fibrillation After Implantation of the Metrix Atroioverter: Observations on Treated and Nontreated Episodes

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OBJECTIVES

We sought to evaluate the number and duration of device-treated and self-terminating, nontreated episodes of atrial fibrillation (AF) after implantation of the Metrix Atroioverter.

BACKGROUND

A recent study has shown that the Atroioverter can rapidly restore sinus rhythm in patients with AF; however, the effect of the device on the clinical course of the arrhythmia in these patients is unknown.

METHODS

The Atroioverter was implanted in 51 patients with symptomatic, recurrent, drug-refractory AF. The device was programmed to periodically monitor the cardiac rhythm. Defibrillation of AF episodes was performed under physician observation.

RESULTS

During a mean follow-up of 260 ± 144 days, 1,161 episodes of AF were observed during valid monitoring periods in 45 of 51 patients. Forty-one patients experienced 231 episodes for which they sought defibrillation therapy. The average duration of the treated episodes during valid monitoring periods (190 of 231 episodes in 39 of 41 patients) was significantly longer than that of the nontreated episodes (38 ± 44 vs. 10 ± 8 h; p < 0.05). The time between episodes requiring Atroioverter therapy increased, and the risk of having an episode requiring treatment decreased. No changes were observed in the number and duration of the short-lasting, nontreated episodes as time since implantation of the device increased.

CONCLUSIONS

In patients with symptomatic, recurrent, drug-refractory AF, the frequency of long-lasting episodes, which were treated under observation with repeated defibrillation using the Atroioverter, decreased. The number and duration of short-lasting, nontreated episodes did not change during the 20-month study period. The effect of ambulatory use of the device on the recurrence of short-lasting episodes needs to be evaluated.

Several nonpharmacologic options are currently available to treat patients with atrial fibrillation (AF). Internal atrial defibrillation using percutaneous transvenous catheter electrodes has been shown to be effective and safe in converting AF to sinus rhythm, using R-wave–synchronized, low energy shocks (1–3). These observations resulted in the development of an implantable atrial defibrillator (Metrix Atroioverter, InControl, Inc., Redmond, Washington). The Atroioverter was recently evaluated in a prospective, multicenter study with the primary objective being the safety and efficacy of the device (4). The Atroioverter, however, is not only able to safely treat episodes of AF, but also to provide information on the incidence and duration of episodes. The aim of this study was to report on 1) the occurrences of AF episodes, treated and nontreated by the Atroioverter; and 2) the effect of repeated intra-atrial defibrillation on the subsequent episodes of AF.

METHODS

Patients. From October 1995 to July 1997, the Atroioverter was implanted in 51 patients with previous episodes of AF that spontaneously terminated or were converted to sinus rhythm with intervals of recurrence between one week and three months. Previous ineffective treatment with at least one class I or III antiarrhythmic drug was required. The exclusion criteria of this prospective, multicenter study have been described previously (4). Concomitant pharmacologic treatment (e.g., anticoagulation, antiarrhythmic drugs) was...
left to the preference of the physician. The Metrix model 3000 was implanted in 17 patients, and the Metrix model 3020 was implanted in the remaining 34 patients. These two devices differ only in defibrillation waveform and output (4).

Patients were instructed to come to the hospital for treatment of each symptomatic episode of AF, where defibrillation was then performed under physician observation. Data pertaining to defibrillation therapy, such as shock characteristics and effectiveness, and clinical factors, such as anticoagulation and antiarrhythmic medication, were recorded. The protocol was approved by the Ethics Committee or Institutional Review Board of each participating center. Written, informed consent was obtained from each patient.

Follow-up. The study ended after the last patient who received an implant completed his three-month, postimplant follow-up. Postimplant clinical follow-up with device interrogation was performed before hospital discharge and at one-month, three-month and six-month intervals thereafter until the completion of the overall study. When the patient sought treatment of a spontaneous episode, device interrogation was also performed.

Definition and determination of AF episodes. Discrete sampling of the cardiac rhythm was performed by the device at periodic intervals. The device was programmed to perform an AF detection every 20 min to 1 h. Each time AF was detected, notation of the date and time of the individual detection was logged to memory. Valid monitoring periods were defined as the time between interrogations of the device, where a printout of the interrogation was made, and the device memory did not overflow owing to too many individual AF detections during this interinterrogation period (i.e., >170 individual AF detections). From the individual detections of AF, the onset and duration of all episodes during valid monitoring periods were reconstructed.

Recently, Tse et al. (5) reported the long-term efficacy results of the AF detection algorithm of the Atrioverter and demonstrated that the algorithm had 100% specificity and 92.3% sensitivity for the detection of AF in the same patient population. As specificity was 100%, the onset of an episode was defined by a single AF detection. As sensitivity was 92.3%, we required at least three consecutive detections as “not AF” before defining the end of an episode. In theory, this method increased the sensitivity to detect the end of an AF episode to >99%. Lastly, we excluded any patient in whom the individual AF detection function did not meet 100% specificity and >90% sensitivity for cut-off.

Statistical analysis. Continuous variables are expressed as the mean value ± SD. The overall goal of this study was to determine if the data supported the hypothesis that the duration between treated AF episodes increases as a function of the time from implantation of the Atrioverter. For each of the statistical analyses used in this study, the unit of analysis is an episode rather than a patient. This is because, in general, each patient has a multiple number of episodes, and the actual number of episodes between patients varies. An efficient mechanism for examining this type of data utilizes all observations within a patient and allows interpatient variability in the estimation used for statistical testing. The methods used in this study provide for these considerations.

A random effects, mixed modeling technique allows for a variable number of repeated observations within the patients and takes into consideration the interpatient variability. The mixed models, random effects technique applied to these data fits a linear function to the relation of episode length to time since implantation, with the slope of this linear function serving as a random effect. In essence, the slope of a given patient’s linear relation is determined individually, and testing of the population slope takes into account the variability between each of the individual patient slopes for their individual relations of episode duration and time since implantation. Because we have multiple observations within patients, the variability associated with the estimated slope variable due to patient can be determined. The statistical test to determine if the slope differs significantly from zero, or equivalently if the mean response significantly differs over time, therefore, allows for any interpatient variability.

For the analysis of the risk of experiencing AF episodes, the multivariate survival analysis described by Prentice et al. (6) was used to compare the hazard or risk of experiencing an episode of AF as a function of time since implantation. This technique allows for the possibility of multiple events within patients, as well as the inclusion of the censored period from the last AF episode to the end of patient follow-up. For all analyses, p <0.05 was statistically significant.

RESULTS

Patients characteristics. The clinical characteristics of the 51 patients are given in Table 1. On average, 3.9 antiarrhythmic drugs were tried before implantation of the device; this includes drugs that were not tolerated and discontinued, in addition to drugs that were only partially effective and continued. At implantation and at the end of the study, eight and three patients, respectively, were not treated with antiarrhythmic drugs. During the study period, 26 (51%) of 51 patients underwent changes in their antiarrhythmic drug regimen. At the end of the study, 32 patients were treated with class III antiarrhythmic agents, singly or in combination with class I or rate-controlling agents, or both. Anti-
arrhythmic treatment at the beginning and at the end of the study period is shown in Table 2.

Before implantation, 34 patients (67%) were taking warfarin or heparin, 9 (18%) were treated with aspirin and 8 (16%) were not receiving anticoagulation therapy. During the course of the study, 11 patients (22%) had changes in their anticoagulation therapy. One patient discontinued warfarin therapy, five patients were changed from warfarin to aspirin and five patients were started on warfarin. At the end of the study, 13% of patients were not taking any form of anticoagulation and an additional 23% were taking only aspirin. No thromboembolic events occurred during the course of the study.

Frequency and duration of AF episodes in patients with the Atrioverter. During a follow-up of 260 ± 144 days, 45 of the 51 patients had 1,230 episodes of AF recorded in the device’s memory. Five patients had no episodes recorded during a mean follow-up of 164 ± 112 days, and one patient was excluded owing to known AF detection problems. In 41 patients, 231 episodes were treated with the device, including the episodes from the patient with AF detection problems. Five patients had episodes in their device’s memory, but received treatment for none of them.

Of the 1,230 episodes, 1,161 occurred during valid monitoring periods (Table 3). The average recurrence rate was 3.9 ± 5.0 episodes per patient-month. Of the 231 treated episodes, 190 occurred during valid monitoring periods in 39 of 45 patients. Six patients had no treated episodes during valid monitoring periods. This includes the five patients who had no treated episodes at all and one patient who had only treated episodes that occurred during nonvalid monitoring periods.

The number and duration of the treated and nontreated AF episodes according to time since implantation are shown in Table 4. The number of nontreated episodes did not change; however, the number of treated episodes decreased. The median duration of the treated episodes was 17.6 h, and for the nontreated episodes, 3 h (mean 38 ± 44 h vs. 10 ± 18 h; p < 0.05). In addition, 78% of the nontreated episodes were <8 h in length, as compared with only 28% of treated episodes.

When the distribution of the AF episodes that occurred during valid monitoring periods was analyzed according to the percentage of treated episodes, the following observations were made (Table 3). In 15 (33%) of the 45 patients,
81% of the AF episodes were treated, and in eight of these patients, the AF episodes were always treated. The AF episodes occurring within a valid monitoring period from 19 patients (42%) were either not treated at all (six patients with 37 episodes) or treated in 10% of episodes (13 patients with 835 episodes).

Effect of Atrioverter therapy on the interval between spontaneous episodes of AF. To evaluate the time course of symptomatic, treated AF episode frequency, we evaluated the duration between treated AF episodes and the risk of having an episode as time since implantation increased. For all these analyses, the follow-up intervals of the patients were measured relative to the day of implantation. The result of the first mixed models analysis is shown in Figure 1. The goal of this exploratory analysis was to examine the mean length of time during which no AF was observed, categorized by the number of days since implantation that the next treated episode occurred. Only patients with two or more spontaneous episodes for which therapy with the Atrioverter was sought were included (n = 33). In addition, we only considered intervals between episodes where the actual time was observed (i.e., we excluded from the analysis the time from a patient’s last episode to the end of the study). As seen in Figure 1 and the predicted line, there appears to be a relation between the mean time between treated episodes and time since implantation (p < 0.05). That is, as time since implantation increases, the mean interval between treated episodes also increases.

A graphic evaluation of the change of the risk of having an episode requiring Atrioverter treatment is shown in Figure 2. For this, all patients who had at least one treated episode were included (n = 41). For a given period since implantation, the number of patients at risk for an episode was determined (i.e., the number of patients actively enrolled in the study). The estimated risk was then calculated as the ratio of the number of patients who had at least one treated episode during the given period to the number of patients at risk. As can be seen in Figure 2, the risk of observing an episode decreased as time since implantation increased.

Lastly, for patients who had at least one episode (n = 41), multivariate survival analysis was performed to examine the

![Figure 1](image-url). There was an increase of the mean interval between treated spontaneous AF episodes as time since implantation of the Atrioverter increased. Solid line = observed mean and standard error of the interval between treated spontaneous AF episodes; dashed line = predicted mean of the interval between treated spontaneous AF episodes.

<table>
<thead>
<tr>
<th>Days Since Implantation</th>
<th>Nontreated AF Episodes</th>
<th>Treated AF Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Duration (h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>0–50</td>
<td>213</td>
<td>7.5 ± 15.7</td>
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<tr>
<td>51–125</td>
<td>261</td>
<td>11.6 ± 20.3</td>
</tr>
<tr>
<td>126–200</td>
<td>224</td>
<td>8.2 ± 19.1</td>
</tr>
<tr>
<td>&gt;200</td>
<td>273</td>
<td>12.1 ± 15.0</td>
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AF = atrial fibrillation; n = number of atrial fibrillation episodes.
over time. We found that there was no increase in the duration of the nontreated episodes would increase. As time since implantation increased, the risk of a treated spontaneous AF episode decreased.

hazard or risk of experiencing an AF episode as time since implantation increased. In general, this technique stratifies the data by episode number, where the response is the time between treated episodes and the number of days since implantation is considered as a possible explanatory variable. This analysis then tests, over strata, whether the risk of experiencing an episode depends on the number of days since implantation. It was shown that the hazard of experiencing an episode decreased as time since implantation increased ($p < 0.05$) (Table 5). On the basis of this analysis, the risk of experiencing an episode of AF requiring defibrillator therapy 60 days after implantation was reduced by 73%, as compared with the risk of experiencing an episode of AF seven days after implantation.

One other aspect that we evaluated was whether the nontreated episodes had any impact on the prolongation of the time between treated episodes of AF, and whether this was caused by the patient’s reluctance to have Atrioverter therapy. To explore this, the durations of the treated and nontreated episodes were compared as time since implantation increased. The basis for the use of this comparison is that because the treated episodes were of longer duration, as mentioned previously, and if potentially treatable episodes of longer duration went untreated based on the patient’s reluctance to have Atrioverter therapy, the mean and median duration of the nontreated episodes would increase over time. We found that there was no increase in the duration of the nontreated episodes over time ($p > 0.05$). In fact, the number of nontreated episodes neither increased nor diminished over time ($p > 0.05$).

**DISCUSSION**

**Natural history of AF.** The paroxysmal nature of AF in this patient group is demonstrated by the presence of multiple episodes of the arrhythmia during the 20-month follow-up period. Although only patients with estimated arrhythmia recurrence intervals between one week and three months were eligible for inclusion, 5 of the 51 patients had no episodes of AF during a mean follow-up duration of 164 ± 112 days. This may be explained by the natural history of the arrhythmia in these patients. In addition, none of the patients who had the device implanted at the time of the end of the study had progressed to chronic, permanent AF.

Forty-five patients had >1,000 spontaneous AF episodes during the follow-up period. In patients with both treated and nontreated episodes, the treated episodes had a significantly longer duration than the nontreated ones. This is partially due to the fact that patients had to return to the hospital for treatment, often requiring >1 h of transportation, or that these nontreated episodes may have been asymptomatic. When the spontaneous AF episodes were classified according to 8-h duration, it was observed that 72% of the nontreated episodes were <8 h, whereas 78% of the treated episodes were >8 h in duration. These data suggest that there are patients who have both episodes of long duration requiring treatment as well as short or asymptomatic episodes that are well tolerated or may go ignored. Whether these short-lasting, nontreated episodes affect the need for anticoagulation in the patient with an Atrioverter remains unknown. Most patients in this study were anticoagulated and no thromboembolic events were seen, despite these nontreated episodes, and therefore, no conclusions can be drawn. However, when patients are able to treat episodes with the Atrioverter outside the hospital, more of the shorter duration episodes may be treated and, thus, may have an impact on the need for anticoagulation.

**Reversion of long-term changes.** An experimental study in chronically instrumented goats has shown that AF induces changes in the electrophysiologic properties of the atria, which may lead to the development of chronic AF (electrical remodeling) (7). This animal study suggested interruption of the arrhythmia as soon as possible to prevent subsequent AF episodes. The electrical atrial remodeling completely reverted within one week after restoration of sinus rhythm in the goats. The question that can be asked of the data from the present study is whether the electrical atrial remodeling has changed (reflected by a decrease in the number of AF episodes) after repeated intra-atrial defibrillation of our patients with a long history of AF. If we take both treated and nontreated AF episodes into consideration, it seems that no reversion of the atrial electrical remodeling has occurred at this point of follow-up. However, one must

**Table 5. Reduction in the Risk of a Treated Atrial Fibrillation Episode Relative to Day 7 After Atrioverter Implantation**

<table>
<thead>
<tr>
<th>Days Since Implantation</th>
<th>Reduction in Risk</th>
</tr>
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<tbody>
<tr>
<td>14</td>
<td>16.7%</td>
</tr>
<tr>
<td>30</td>
<td>44.5%</td>
</tr>
<tr>
<td>60</td>
<td>73.1%</td>
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<tr>
<td>90</td>
<td>86.3%</td>
</tr>
<tr>
<td>120</td>
<td>92.6%</td>
</tr>
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</table>
also consider that a majority of these nontreated episodes (803 episodes) were from only 13 patients, potentially skewing the data. When only the treated episodes (190 episodes) were analyzed, the mean interval between these AF episodes increased as time since implantation increased, potentially denoting some form of reversion of electrical remodeling. The unchanged frequency of nontreated episodes demonstrates that the increase in time between treated episodes cannot be fully explained by the patient’s reluctance to have Atrioverter therapy. The reason why the number of the nontreated or short-lasting episodes did not decrease over time is not yet understood. Perhaps, with the ambulatory use of the device in either an automatic mode (with defibrillation after a fixed time from the onset of the episode) or a patient-activated mode, these short-lasting episodes will also be treated and decrease over time.

**Study limitations.** Antiarrhythmic drugs could have played a role in affecting the number, frequency and duration of AF episodes after implantation of the device. As the use of these agents was not controlled in this study, no evaluation of their effect on possible reversibility of remodeling could be made from these data about the episodes. Future studies will be needed to separate the relative contributions of antiarrhythmic drug use and repeated defibrillation therapy.

Symptoms were not collected from the patients during the study. Therefore, it could not be determined whether the nontreated episodes were asymptomatic and what the time of onset of symptoms to device treatment was.

**Conclusions.** In patients with symptomatic, recurrent, drug-refractory AF, the frequency of long-lasting episodes treated with repeated defibrillation using the Atrioverter decreased. The number and duration of short-lasting, nontreated episodes did not change during the 20-month study period. Prompt termination of all episodes of AF using out-of-hospital treatment with the Atrioverter needs to be evaluated.

**APPENDIX**

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**REFERENCES**


