Success of serial external electrical cardioversion of persistent atrial fibrillation in maintaining sinus rhythm

A randomized study

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Aims The aim of this prospective, randomized study was to determine the efficacy of a serial external electrical cardioversion strategy in maintaining sinus rhythm after 12 months in patients with recurrent persistent atrial fibrillation.

Methods and Results Ninety patients with persistent atrial fibrillation lasting more than 72 h but less than 1 year were randomized in a one to one fashion to repetition of up to two electrical cardioversions in the event of relapse of atrial fibrillation detected within 1 month of the previous electrical cardioversion (Group AGG), or to non-treatment of atrial fibrillation relapse (Group CTL). ECGs were scheduled at 6 h, 7 days, and 1 month. Clinical examination and ECGs were repeated during the 6-month and 12-month follow-up examinations. Echocardiography was repeated during the 6-month follow-up examination. Clinical and echocardiographic characteristics were similar in the two groups. All patients were treated with antiarrhythmic drugs before electrical cardioversion and throughout follow-up. After 12 months, sinus rhythm was maintained in 53% of Group AGG patients and in 29% of Group CTL patients (P<0.03). After 6 months, left ventricular ejection fraction had recovered significantly only in Group AGG (56.8 ± 9.0% at enrolment vs 60.4 ± 9.4% at 6 months, P<0.001).

Conclusion These results demonstrate that an aggressive policy towards persistent atrial fibrillation by means of repetition of electrical cardioversion after early atrial fibrillation recurrence is useful in maintaining sinus rhythm after 12 months. (Eur Heart J, 2002; 23: 1522–1528, doi:10.1053/euhj.2002.3167) © 2002 The European Society of Cardiology. Published by Elsevier Science Ltd. All rights reserved.

Key Words: Atrial fibrillation; electrical cardioversion.

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Introduction

Atrial fibrillation is a very common arrhythmia, which increases in prevalence in patients >60 years old[1,2]. Over time, it tends to become persistent or permanent, even if no underlying structural heart disease is present[11,2]. The success rate of electrical cardioversion and the maintenance of sinus rhythm are highly dependent on the duration of the previous atrial fibrillation episode[3–5]. After electrical cardioversion only 20–40% of patients maintain sinus rhythm for the first year[6–8].

The highest incidence of recurrences is seen during the first month after cardioversion, particularly within the first 5 days[9]. The mechanism of early relapses seems to be different from that of late recurrences.

A possible explanation for early relapses is remodeling of the atria: atrial fibrillation itself causes progressive electrophysiological and structural changes to the atria and modification of autonomic innervation, which initiates or perpetuates atrial fibrillation[10–15].

Serial electrical cardioversion is often used to maintain sinus rhythm in patients with persistent atrial fibrillation. However, its usefulness has never been established in a randomized manner[16,17]. In particular, it has never been ascertained whether repetition of cardioversion soon after early relapses facilitates long-term persistence of sinus rhythm.
The aim of this prospective, randomized study was to determine the efficacy of serial external electrical cardioversion in maintaining sinus rhythm after 12 months in patients with recurrent persistent atrial fibrillation.

Methods

From January 1999 to May 2000, 193 patients with persistent (duration >72 h) atrial fibrillation were referred to our department to undergo elective electrical cardioversion.

Electrical cardioversion

On inclusion in the waiting list for elective electrical cardioversion, each patient’s clinical and pharmacological history was collected, and physical examination, ECG, chest X-ray, and echocardiogram were performed. All patients received oral anticoagulant for at least 4 weeks before and 4 weeks after the cardioversion.

Elective electrical cardioversion was planned after 4 weeks. Meanwhile, atrial fibrillation was confirmed by intermittent ECG.

Electrical cardioversion was performed under general anaesthesia with intravenous propofol or thiopental in fasting patients. Shock was delivered by means of external paddles positioned in the anterior–apex position connected to an external cardioverter (CardioServ — Hellige Inc. Freiburg, Germany). The first shock was delivered at 300 J. If the first attempt at cardioversion failed, shock was delivered in the antero-posterior position at 360 J.

Electrical cardioversion was deemed successful if sinus rhythms were continuously recorded for 5 min after the shock. Cardioversion was successful in 170 patients (88%).

To be eligible for the study, patients had to have had at least one previous successful external electrical cardioversion for persistent atrial fibrillation, and had to be on treatment with Class IC or Class III antiarrhythmic drugs.

Exclusion criteria

The exclusion criteria were as follows: atrial fibrillation known to have been present continuously for more than 12 months; more than two electrical cardioversions in the previous 6 months; a left atrial diameter larger than 60 mm; myocardial infarction during the previous 3 months; cardiac surgery during the previous 30 days; atrial fibrillation associated with an acute reversible condition; presence of a VVI pacemaker; age less than 18 years; any medical condition that would make survival for 1 year unlikely.

Randomization

After written consent had been obtained, patients were randomly assigned in a one to one fashion to up to two repetitions of electrical cardioversion in the event of relapse of atrial fibrillation detected within 1 month of the previous cardioversion (Group AGG), or to non-treatment of atrial fibrillation relapses (Group CTL).

Echocardiographic analysis

Transthoracic two-dimensional imaging and pulsed Doppler echocardiography were performed using Hewlett-Packard Sonos 1500 or 2000 ultrasound machines equipped with 2·5 and 3·5 Mhz phased-array transducers (Hewlett-Packard Co. — Andover, MA., U.S.A.) before atrial fibrillation termination and after 6 months. Left ventricular ejection fraction was determined by calculating the end-diastolic and end-systolic volumes according to Folland et al.[18]. Left atrial size was measured at end-systole in the parasternal long-axis view.

Follow-up

ECGs were scheduled at 6 h, 7 days, and 1 month after each cardioversion, and whenever patients referred palpitations. After 6 months, clinical examination, ECG, and echocardiography were repeated, and the Minnesota Living with Heart Failure Questionnaire was administered[19]. After 12 months, clinical examination, and ECG were repeated.

Only ECG-documented atrial fibrillation was counted as recurrence.

Statistical analysis

Continuous variables are presented as means (SD). Discrete variables are presented as percentages (%). Analyses were performed according to the intention-to-treat principle. For comparison of groups, continuous variables were tested using two-tailed Student’s t-test for unpaired data; discrete variables were tested using the chi-square test or Fisher’s exact test. For comparison of continuous variables within the same group between the enrolment and the end of the follow-up, two-tailed Student’s t-test for paired data was used. A P value <0·05 was considered statistically significant.

Results

Baseline characteristics

A total of 90 patients were enrolled: 45 in Group AGG, and 45 in Group CTL.

Clinical and echocardiographic characteristics of the study groups at the time of enrolment are shown in Table 1. There were no significant differences in baseline.
Characteristics between the two groups. Nevertheless, Group CTL patients had had more previous electrical cardioversion than Group AGG patients (1.36 ± 0.74 vs 1.84 ± 1.59, \( P = 0.07 \)). However, the median of previous electrical cardioversion was 1 for both groups (range: 1–4 Group AGG and 1–10 Group CTL).

### Adverse events

All electrical cardioversions were performed without complications. A total of three adverse events were recorded (3.3%) during the follow-up. One Group AGG patient and one Group CTL patient died after the first month of follow-up, and one Group AGG patient suffered a stroke.

### Early recurrences of atrial fibrillation

Atrial fibrillation relapsed in 36 of 90 patients (40%) during the first 30 days of follow-up: in one patient (1%) within 6 h, and in 25 patients (28%) within 7 days of cardioversion. The incidence of atrial fibrillation recurrence at 7 days and at 30 days was no different between the two groups (29% Group AGG vs 29% Group CTL at 7 days, and 38% Group AGG vs 42% Group CTL at 30 days, \( P = 1.00 \)).

### Electrical cardioversion repetitions

A mean of 1.47 ± 0.76 electrical cardioversions per patient were performed in Group AGG patients. Electrical cardioversion was repeated in 14 of 45 Group AGG patients (31%). The mean time in atrial fibrillation prior to second cardioversion was 29.8 ± 23.7 days (range 2–60 days). Atrial fibrillation relapsed again in eight of these 14 patients (57%): in one patient (7%) within 6 h, and in seven patients (50%) within 7 days of the second cardioversion.

A third electrical cardioversion was performed in seven of 45 Group AGG patients (16%). The mean time in atrial fibrillation prior to third cardioversion was 22.3 ± 24.2 days (range 4–70 days). Atrial fibrillation relapsed again in one patient (14%) within 6 h and in five patients (71%) within 7 days of the third cardioversion. There were no significant differences in clinical or echocardiographical variables between the six patients who had three early relapses and all the other patients.

It is noteworthy that the six patients in whom atrial fibrillation did not relapse within 7 days of the second cardioversion, maintained sinus rhythm at the 12-month follow-up examination. The time interval between the first atrial fibrillation relapse and the second cardioversion was similar in patients who had a second recurrence and in patients who maintained sinus rhythm until the 12-month follow-up examination (30.9 ± 23.2 and 28.3 ± 26.5 days respectively, \( P = 0.85 \)).

### Cross-over

A total of five cross-overs were observed (6%). One Group CTL patient repeated the electrical cardioversion 3 days after a symptomatic atrial fibrillation relapse.

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**Table 1 Comparison of clinical and echocardiographical characteristics of patients at the time of enrolment**

<table>
<thead>
<tr>
<th></th>
<th>Group AGG (n=45)</th>
<th>Group CTL (n=45)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.0 ± 7.6</td>
<td>69.0 ± 9.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>64</td>
<td>64</td>
<td>1.00</td>
</tr>
<tr>
<td>Underlying heart disease (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>9</td>
<td>18</td>
<td>0.18</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>42</td>
<td>38</td>
<td>0.83</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>9</td>
<td>2</td>
<td>0.18</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>11</td>
<td>20</td>
<td>0.19</td>
</tr>
<tr>
<td>Lone AF</td>
<td>29</td>
<td>22</td>
<td>0.63</td>
</tr>
<tr>
<td>AF history (months)</td>
<td>31.6 ± 3.4</td>
<td>39.9 ± 3.6</td>
<td>0.27</td>
</tr>
<tr>
<td>Previous electrical cardioversions (n)</td>
<td>1.36 ± 0.74</td>
<td>1.84 ± 1.59</td>
<td>0.07</td>
</tr>
<tr>
<td>AF episode duration (days)</td>
<td>73.4 ± 63.9</td>
<td>75.9 ± 39.7</td>
<td>0.85</td>
</tr>
<tr>
<td>Medications (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>60</td>
<td>69</td>
<td>0.51</td>
</tr>
<tr>
<td>Verapamil</td>
<td>22</td>
<td>16</td>
<td>0.59</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>7</td>
<td>0</td>
<td>0.12</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>64</td>
<td>67</td>
<td>1.00</td>
</tr>
<tr>
<td>Sotalol</td>
<td>4</td>
<td>4</td>
<td>1.00</td>
</tr>
<tr>
<td>Propafenone/Flecainide</td>
<td>31</td>
<td>27</td>
<td>0.82</td>
</tr>
<tr>
<td>Left atrial size (mm)</td>
<td>47.6 ± 5.1</td>
<td>48.6 ± 6.5</td>
<td>0.44</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter (mm)</td>
<td>53.1 ± 5.8</td>
<td>53.7 ± 5.6</td>
<td>0.61</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>56.8 ± 9.0</td>
<td>56.1 ± 9.1</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD), unless otherwise indicated.*More than one per patient possible. AF=atrial fibrillation.
occurred within 7 days of the first electrical cardioversion. Atrial fibrillation relapsed again after 7 days. Among Group AGG patients, three patients refused to undergo the second electrical cardioversion, and one refused to undergo the third cardioversion.

**Late recurrences of atrial fibrillation**

Atrial fibrillation relapsed between the first and the twelfth month of follow-up in 27 of 90 patients (30%). There was no difference between the two groups (29% Group AGG vs 31% Group CTL, $P=0.83$).

**Maintenance of sinus rhythm**

After 6 months, sinus rhythm was maintained in 35 of 45 Group AGG patients and in 21 of 45 Group CTL patients (78% Group AGG vs 47% Group CTL; $P<0.005$). The difference was still statistically significant after 12 months, when 24 of 44 Group AGG patients and 13 of 44 Group CTL patients were in sinus rhythm (55% Group AGG patients vs 30% Group CTL patients, $P<0.03$). (Figure 1).

After 12 months, antiarrhythmic treatments were similar between the two Groups, apart from digoxin, which was more frequently administered in Group CTL patients (Table 2). By contrast, a significantly higher percentage of Group CTL patients were on anticoagulation therapy (23% Group AGG vs 55% Group CTL, $P<0.004$).

**Echocardiographic analysis**

At the time of enrolment there were no significant differences between the two Groups in terms of left atrial size, left ventricular end-diastolic diameter, and left ventricular ejection fraction (see Table 1). At the 6-month follow-up examination, echocardiography could not be repeated in five patients (two Group AGG and three Group CTL), and their data were withdrawn from the analysis. Left atrial size, left ventricular end-diastolic diameter, and left ventricular ejection fraction were still not significantly different between the two groups. However, in Group AGG patients, left ventricular ejection fraction improved significantly from $56.8 \pm 9.0\%$ to $60.4 \pm 9.4\%$ ($P<0.001$), while in Group CTL patients left ventricular ejection fraction was unchanged ($56.1 \pm 9.1\%$ on enrolment vs $56.3 \pm 10.6\%$ after 6 months, $P=0.10$).

**Quality of life**

The Minnesota Living with Heart Failure Questionnaire score did not show any significant difference between the two groups after 6 months ($8.0 \pm 7.6$ Group AGG vs $11.7 \pm 17.0$ Group CTL, $P=0.20$). However, the score was significantly lower in patients who maintained sinus rhythm than in patients in whom atrial fibrillation relapsed ($7.3 \pm 8.5$ sinus rhythm vs $15.2 \pm 18.7$ atrial fibrillation, $P<0.02$).

**Discussion**

For the first time, an aggressive policy towards persistent atrial fibrillation treatment by means of electrical cardioversion repetition after early recurrence has been demonstrated to be useful in maintaining sinus rhythm after 12 months.

This is the first study in which the usefulness of serial external electrical cardioversion in maintaining sinus rhythm has been evaluated in a randomized manner. Moreover, in previous studies, either the follow-up duration was short or cardioversion was associated to serial antiarrhythmic drug treatments[16,20,21]. Van Gelder et al. followed up for 3·7 ± 1·6 years 236 patients after a first episode of atrial fibrillation lasting more than 24 h[16]. After 12 months, about 15% of patients who had not repeated electrical cardioversion were in sinus rhythm, as against 40% of patients who had undergone more than one cardioversion. No further advantage in terms of maintenance of sinus rhythm was observed after the forth electrical cardioversion.

More recently, a policy of early repeated internal electrical cardioversion was evaluated in 45 patients with persistent atrial fibrillation and without antiarrhythmic medication.

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**Figure 1** The atrial fibrillation-free survival curves of Group AGG ($\bullet$) and Group CTL (■) patients during the study period are presented. $^*P<0.005$ Group AGG vs Group CTL; $^\wedge P<0.03$ Group AGG vs Group CTL.

**Table 2** Comparison of antiarrhythmic treatment after 12 months of follow-up

<table>
<thead>
<tr>
<th>Medications (%)</th>
<th>Group AGG (n=44)</th>
<th>Group CTL (n=44)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulant</td>
<td>23</td>
<td>55</td>
<td>0.004</td>
</tr>
<tr>
<td>Digoxin</td>
<td>36</td>
<td>58</td>
<td>0.05</td>
</tr>
<tr>
<td>Verapamil</td>
<td>16</td>
<td>9</td>
<td>0.26</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>4</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>Amiodarone/sotalol</td>
<td>73</td>
<td>64</td>
<td>0.48</td>
</tr>
<tr>
<td>Propafenone/flecainide</td>
<td>31</td>
<td>29</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*More than one per patient possible.
treatment[22]. Up to three internal electrical cardioversions were performed as soon as possible after atrial fibrillation relapse, and patients were followed up for 1 month. Despite evidence of reversal of atrial electrical remodelling, only 17% of those patients who repeated internal electrical cardioversion maintained sinus rhythm for 1 month. By contrast, of the patients who repeated cardioversion in our study, 50% were in sinus rhythm at the 12-month follow-up examination. The absence of antiarrhythmic treatment and the longer mean duration of atrial fibrillation in patients enrolled by Fynn et al. might explain this discrepancy.

At the same time, our results showed that repetition of more than one electrical cardioversion after early atrial fibrillation recurrence has limited clinical value. Indeed, sinus rhythm was maintained in 43% of patients who repeated only one cardioversion, while only one of the seven patients (14%) who repeated the second cardioversion was in sinus rhythm after 1 week.

Early recurrences of atrial fibrillation

Findings from this study confirm the high rate of atrial fibrillation recurrence within the first days after conversion to sinus rhythm. Indeed, atrial fibrillation relapsed within the first week in 28% of patients, despite an optimal antiarrhythmic treatment. Atrial remodelling has been proposed as the mechanism responsible for these early atrial fibrillation recurrences[10–15]. The perturbation of atrial electrophysiological properties, called atrial electrical remodelling, is the most frequently studied among these phenomena, both in animal models and in humans.

Atrial electrical remodelling includes shortening of the atrial effective refractory period, reversal of the physiological rate-adaptation of the refractory period, spatial dispersion of atrial refractoriness, and reduction of conduction velocity[10]. It has been demonstrated to begin a few minutes after atrial fibrillation initiation[12,23]. In patients with persistent atrial fibrillation, recovery from atrial electrical remodelling ranged from 12 to 72 h[23–25]. Thus, the useful effect of our policy in maintaining sinus rhythm does not seem to be related to the prevention of atrial electrical remodelling, as cardioversion was repeated too late after atrial fibrillation recurrence. Indeed, in patients with long-lasting atrial fibrillation, prevention of atrial electrical remodelling by means of prompt repetition of cardioversion did not produce any reduction in atrial fibrillation recurrences. Fynn et al. found a high rate of atrial fibrillation recurrences after prompt execution of the second and third electrical cardioversion (20 and 13 h respectively) despite electrophysiological evidence of reversal of atrial electrical remodelling[22]. The question remains as to what kind of atrial remodelling prevention (ultrastuctural, structural?) might be obtained by our successful serial electrical cardioversion policy[26,25].

The behaviour of the six patients in whom the aggressive policy did not work is interesting. These patients went on to relapse within 7 days of conversion to sinus rhythm despite a shorter duration of atrial fibrillation episodes (Table 3). Thus, a trigger rather than atrial remodelling seems to be the mechanism of repetitive early relapses in these patients. Adoption of this aggressive policy of treatment of early relapses might indirectly help us to select patients with repetitive early relapses, who should be referred to focal trigger elimination by means of radiofrequency transcatheter ablation[28].

Late recurrences of atrial fibrillation

The rate of atrial fibrillation recurrences between the first and the twelfth month was similar in the two study Groups. This is an important finding, as it means that the main result of the study was not affected by differences in the behaviour of the study patients during the long-term follow-up.

Echocardiographic findings

Atrial fibrillation per se has been reported to be detrimental to left ventricular function. Loss of atrial contribution to ventricular filling, irregularity of ventricular contraction, and high heart rate lead to impairment of cardiac output[29–32]. Regularization of ventricular rhythm by means of atrioventricular junction ablation is enough to improve left ventricular performance[33].

It has already been reported that conversion to sinus rhythm of chronic atrial fibrillation can substantially increase left ventricular ejection fraction in patients with idiopathic dilated cardiomyopathy[34]. In our patients, despite a mean duration of the atrial fibrillation episode of about 5 months and the presence of an underlying heart disease in 75%, the mean left ventricular ejection fraction presented only a mild reduction (56.5 ± 9.0%). After 6 months, left ventricular ejection fraction had recovered significantly only in Group AGG patients, while it remained unchanged in Group CTL patients. This result confirmed the usefulness of maintaining sinus rhythm in order to improve left ventricular function.

Quality of life

Previous studies on quality of life assessment in atrial fibrillation patients demonstrated that several aspects of

### Table 3 Relation between duration of atrial fibrillation episodes and rate of relapses within 7 days in the 6 patients in whom the aggressive policy failed

<table>
<thead>
<tr>
<th>EC</th>
<th>Atrial fibrillation duration* (days)</th>
<th>Relapses within 7 days (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>91.7 ± 13.2 (20–360)</td>
<td>100</td>
</tr>
<tr>
<td>2nd</td>
<td>26.2 ± 23.6 (5–40)</td>
<td>100</td>
</tr>
<tr>
<td>3rd</td>
<td>23.5 ± 26.3 (4–70)</td>
<td>100</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD (range). EC=electrical cardioversion.
quality of life may be reduced, even in patients who did not refer symptoms relevant to atrial fibrillation\(^{35,36}\). In our study, the Minnesota Living with Heart Failure Questionnaire administered 6 months after electrical cardioversion showed that quality of life was significantly lower in atrial fibrillation patients than in patients who maintained sinus rhythm, while there was a non-significant difference between Group CTL and Group AGG patients.

In contrast, in the PIAF fibrillation study patients randomized to ventricular rate control, despite a significant reduction in functional activity, did not report an impairment of quality of life as evaluated by means of the SF-36 questionnaire\(^{37}\). This result might be explained by the fact that in the PIAF study not all patients randomized to rhythm control maintained sinus rhythm, and conversely not all patients randomized to rate control were in atrial fibrillation at the end of follow-up.

**Clinical implications**

A large-scale, multicentre trial is investigating whether maintenance of sinus rhythm is superior to rate control of atrial fibrillation in terms of mortality and morbidity\(^{38}\). Meanwhile, findings from the present study demonstrate for the first time that repetition of electrical cardioversion after early recurrence of atrial fibrillation increases persistence of sinus rhythm even after 12 months. Repetition of more than one cardioversion after early atrial fibrillation relapse has no clinical benefit.

Quality of life and left ventricular function are also positively influenced by maintenance of sinus rhythm. Obviously, this study does not answer the question of whether maintenance of sinus rhythm is associated with a reduction in atrial fibrillation-related morbidity and mortality.

**Study limitations**

Unfortunately, the original design of the study did not include echocardiographic evaluation at the 12-month follow-up examination. Thus, we cannot demonstrate the persistence, or even the increase, of left ventricular ejection fraction recovery in Group AGG patients.

The statistical power of the study was calculated to obtain a significant result in terms of maintenance of sinus rhythm after 12 months, which was the main aim of the study. Thus, the lack of a significant improvement in quality of life score and in echocardiographical variables in Group AGG patients compared with Group CTL patients might be due to an insufficient number of patients enrolled.

This study did not investigate the role of electrical cardioversion repetition after late recurrence of atrial fibrillation.

**References**


