Oral amiodarone increases the efficacy of direct-current cardioversion in restoration of sinus rhythm in patients with chronic atrial fibrillation

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Aims Direct current cardioversion of persistent atrial fibrillation is one of the most widely used and effective treatments for the restoration of sinus rhythm, but may be hampered by a low success rate and a high percentage of early recurrence. Pre-treatment with amiodarone or a glucose-insulin-potassium solution could improve the efficacy of electrical cardioversion by reversing the partially depolarized diastolic potential of the subsidiary pacemakers in atrial fibrillation. In a controlled randomized study, we assessed the effectiveness of electrical cardioversion in patients with persistent atrial fibrillation after pre-treatment with amiodarone or potassium infusion and the efficacy of amiodarone in maintaining sinus rhythm after electrical cardioversion.

Methods and Results Ninety-two patients with persistent atrial fibrillation (>2 weeks duration) were prospectively randomized into three matched groups: A (n = 31, oral amiodarone 400 mg . day⁻¹ 1 month before and 200 mg . day⁻¹ 2 months after cardioversion), B (n = 31, 180 mg . day⁻¹ oral diltiazem 1 month before and 2 months after cardioversion and 80 mmol potassium, 50 UI insulin in 500 ml 30% glucose solution 24 h before cardioversion) and C (n = 30, control patients, 180 mg . day⁻¹ oral diltiazem 1 month before and 2 months after cardioversion). Before cardioversion all patients were under 4 weeks effective oral anticoagulant therapy (warfarin). Before electrical cardioversion, the rate of spontaneous conversion to sinus rhythm was higher in group A (25%) than groups B (6%) or C (3%) (P<0·005). Electrical cardioversion was more successful in group A (88%) than groups B (56%) or C (65%) (P<0·05), while the electrical thresholds for effective cardioversion were lower in group B than the other groups (P<0·05). Twenty-four hours after cardioversion, the early recurrence of atrial fibrillation was similar in the three groups (P=ns), while at 2 months the recurrence rate was lower in group A (32%) than groups B (56%) or C (52%) (P<0·01).

Conclusion Pre-treatment with low-dose oral amiodarone, compared with oral diltiazem or glucose-insulin-potassium treatments, induces a significantly high percentage of instances of spontaneous conversion, increases electrical cardioversion efficacy and reduces atrial fibrillation recurrence.

Key Words: Amiodarone, atrial fibrillation, atrial remodelling, electrical conversion, potassium, diltiazem.

See page 11 for the Editorial comment on this article

Introduction

Direct-current cardioversion of atrial fibrillation is one of the most widely used and effective treatments for the restoration of sinus rhythm[1–3]. However, the efficacy of direct-current is limited by a low success rate[4] and by the electrical instability post-cardioversion, which can induce recurrences, particularly in patients with long lasting atrial fibrillation[5,6]. At 12 months after a successful direct-current shock, only 25% of the patients are still in sinus rhythm[7]. Prophylactic antiarrhythmic therapy has been proposed to increase the rate of success and to avoid recurrences, but with controversial results. Maintenance therapy with class I antiarrhythmic drugs, such as quinidine, is commonly employed but with a 50% recurrence rate at 1 year[8]. In addition this class of drugs presents risks of proarhythmia, heart failure and non-cardiac toxicity[9].

New electrophysiological findings have recently suggested possible alternative therapies to increase the rate of successful direct-current conversion and to
reduce atrial fibrillation recurrence. Persistent atrial fibrillation, with sustained rapid atrial rates, is associated with a progressive decrease in atrial refractoriness due to so-called ‘electrical remodelling’, which has been hypothesized to be related to a depletion in high energy phosphates, activation of adenosine triphosphate-sensitive potassium channels and/or overload in cytosolic calcium[10,11].

Antiarrhythmic class III drugs, such as amiodarone, by prolonging atrial refractoriness[12-19] or infusion of glucose insulin potassium solution, by counteracting the diastolic depolarization related to depletion of intracellular potassium[20-24], may reverse the electrophysiological effect of the electrical remodelling, thus affecting the efficacy of direct-current cardioversion.

The aim of this study was to investigate in a randomized, controlled fashion whether the efficacy of direct-current conversion on persistent atrial fibrillation could be affected by pre-treatment with oral amiodarone or with a short-term glucose-insulin–potassium infusion. In particular we evaluated the efficacy of the pre-treatment on the success rate of cardioversion, on the atrial defibrillation threshold and on the maintenance of sinus rhythm at 24 h and after 2 months follow-up. The control group of patients was treated with calcium channel blocker therapy (diltiazem), to control the ventricular response during the arrhythmia, thus avoiding the occurrence of the so-called tachy-cardiomyopathy and improving patients’ symptoms but without any known effect on sinus rhythm conversion[25,29].

Table 1  Clinical characteristics of the patients at the study entry: no significance differences between the three study groups

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone</th>
<th>GIK</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>31</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 ± 15</td>
<td>60 ± 12</td>
<td>58 ± 10</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>16/15</td>
<td>16/15</td>
<td>14/16</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>45 ± 7</td>
<td>42 ± 8</td>
<td>46 ± 5</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>49 ± 8</td>
<td>51 ± 7</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>AF duration (weeks)</td>
<td>16·3 ± 6</td>
<td>17·2 ± 4</td>
<td>18·0 ± 5</td>
</tr>
<tr>
<td>Ventricular rate (beats . min⁻¹)</td>
<td>112 ± 6</td>
<td>108 ± 7</td>
<td>109 ± 5</td>
</tr>
<tr>
<td>Body mass index (m²)</td>
<td>1·8 ± 0·1</td>
<td>1·8 ± 0·2</td>
<td>1·9 ± 0·1</td>
</tr>
<tr>
<td>Cardio concomitant disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No heart disease</td>
<td>11</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Arterial hypertension (n)</td>
<td>13</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Ischaemic heart disease (n)</td>
<td>4</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Dilated cardiomyopathy (n)</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Valvular heart disease (n)</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>FT3 (pg . ml⁻¹)</td>
<td>3·1 ± 0·3</td>
<td>3·5 ± 0·2</td>
<td>3·2 ± 0·3</td>
</tr>
<tr>
<td>FT4 (pg . ml⁻¹)</td>
<td>8·2 ± 0·8</td>
<td>9·0 ± 0·9</td>
<td>9·1 ± 1·1</td>
</tr>
<tr>
<td>TSH (mU . ml⁻¹)</td>
<td>8·2 ± 0·8</td>
<td>9·0 ± 0·9</td>
<td>9·1 ± 1·1</td>
</tr>
<tr>
<td>Cardio co-medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>19</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Nitrites</td>
<td>4</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Mean ± SD. AF=atrial fibrillation; FT4=free thyroxin; FT3=free-triiodothyronine; TSH=thyroid stimulant hormone; GIK=glucose-insulin-potassium solution; LA=left atrium; LV=left ventricle; n=number.

Methods

Study population

The study population consisted of 92 consecutive patients in a stable circulatory condition with a first documented episode of chronic persistent atrial fibrillation, referred to our Cardiac Unit for cardioversion. Atrial fibrillation lasting longer than 2 weeks was defined as persistent.

Patient records were scanned for the following clinical data: age, gender, arrhythmia duration, body mass index, history of hypertension or heart diseases. Atrial fibrillation was associated with no heart disease (lone atrial fibrillation), or with ischaemic heart disease, hypertension, idiopathic dilated cardiomyopathy, or valvular heart disease (Table 1). Exclusion criteria included age >75 years, left atrial diameter >55 mm, thyrotoxicosis, pregnancy, acute myocarditis or pericarditis, acute myocardial infarction, uncompensated heart failure (New York Heart Association functional class III–IV), diastolic blood pressure >115 mmHg, history of pulmonary hypertension, unstable hepatic or renal function, amiodarone therapy within the last 12 months, or resting rate <90/min; also excluded were those affected by sick sinus syndrome, bundle-branch block, and QT prolongation [i.e. corrected QT >0·45 s]. All antiarrhythmic drugs administered before inclusion in the study were discontinued for at least >5 half lives.
Informed consent was obtained from all patients before they entered the study. The study protocol was approved by the Local Medical Ethics Committee.

Study design (Fig. 1)

The patients were prospectively randomized into three groups: A, 31 patients treated with 400 mg day\(^{-1}\) oral amiodarone 1 month before electrical conversion; B, 31 patients treated with oral diltiazem 1 month before and with a continuous infusion of glucose–insulin–potassium solution (i.e. 50 UI insulin plus 80 mmol potassium in 500 ml 30% glucose solution, 1.5 ml kg\(^{-1}\) h\(^{-1}\)) 24 h before electrical conversion; C, 30 patients treated with oral diltiazem 1 month before conversion.

For each of the patients in groups B and C, the dosage of diltiazem was progressively adjusted in order to reduce the resting heart rate below 80/min (according to the AFFIRM study protocol\(^2\)). The starting dose was 60 mg tablets three times a day and by daily control of the electrocardiogram, the dosage was progressively increased by 30 mg three times a day until a maximal dosage of 360 mg day\(^{-1}\). In all patients the usual anticoagulation guidelines were followed\(^{28}\).

Direct-current cardioversion was performed in the morning hours with the patient in the fasting and sedate state. After obtaining an electrocardiogram and non-invasive measurement of arterial pressure, the patients were attached to a defibrillator through self-adhesive pads. The anode was placed on the palpable left ventricular apex, while the cathode was placed on the lateral margin of the right scapula. After adequate sedation (propofol i.v. 2 mg kg\(^{-1}\)h\(^{-1}\)), the patients were shocked with ‘R’ wave synchronized discharges starting from 50 joules; the sequence of shocks was 50, 100, 150, 200, 250, 300 and 360 joules. After an unsuccessful shock approximately 1 min intervened before the next attempt. The shocks were given in a successive fashion. The patients were under electrocardiogram telemetry until hospital discharge which was 24 h after the conversion procedure. Non-invasive arterial pressure was evaluated immediately after electrical conversion and before hospital discharge.

In the amiodarone group (group A) plasma levels of free thyroxin, free-triiodothyronine and thyroid stimulating hormone (FT4, FT3 and TSH) were measured at the study entry, 48 h before electrical conversion and at the 2 month follow-up.

After successful electrical cardioversion, group A patients continued oral amiodarone (200 mg day\(^{-1}\)) while groups B and C continued oral diltiazem therapy (at the same dosages as previously determined) in order to prevent too high a heart rate in case of recurrence of atrial fibrillation.

Successful electrical cardioversion was defined as sinus rhythm restoration lasting for at least 1 min after the procedure. An atrial fibrillation recurrence, which occurred within 24 h after successful electrical conversion, was defined as ‘early recurrence’; a 2 month follow-up was performed in order to assess late recurrence.

Statistical analysis

The quantitative variables were expressed as mean ± standard deviation of the mean unless specified as percent (%). To assess the efficacy of the treatment between different groups individual point comparison was assessed by unpaired Student’s t-test. Cox survival analysis comparing the maintenance of sinus rhythm between different groups of patients was performed. In each patient the energy threshold for electrical conversion was computed as a ratio of body mass index (kg m\(^{-2}\)). A \(P\) value of <0.05 was considered statistically significant.

Results

The three study groups were matched as regards numbers of patients, sex, age, left atrial dimension, atrial...
fibrillation duration and body mass index; no significant difference in the underlying heart disease was present between the three patient groups (Table 1). The mean dosage of diltiazem administered in group B was 216 ± 56 mg . day⁻¹ and in group C 220 ± 45 mg . day⁻¹ (P = ns).

In group A, the amiodarone pre-treatment before electrical conversion did not significantly affect the plasma level of FT3, FT4, TSH. In group B the glucose–insulin–potassium infusion did not significantly increase potassium concentrations: 3.9 mEq . L⁻¹ before vs 4.1 mEq . L⁻¹ after infusion (P = ns).

### Atrial fibrillation characteristics

The clinical and electrocardiographic characteristics of the patients with atrial fibrillation at entry into the study are shown on Tables 1 and 2. One month later, before electrical conversion, compared to study entry, both amiodarone and diltiazem treatments significantly decreased mean heart rate but not systolic or diastolic blood pressures. Consequently no significant differences in mean heart rate and systolic/diastolic arterial pressure were observed among the three groups at the different time intervals (Table 2).

### Restoration of sinus rhythm before electrical conversion

Spontaneous conversion to sinus rhythm was achieved in eight out of 31 patients in group A (25%), in contrast with only two patients in group B (6%) or one patient in group C (3%) (P < 0.005 group A vs group B and group C). Because of the small numbers, no subgroup analysis was performed.

#### Restoration of sinus rhythm with electrical conversion

The electrical conversion was performed in the remaining 81 patients, with overall sinus rhythm restoration in 56 patients (69%); pre-treatment with amiodarone (group A) resulted in restoration of sinus rhythm in 20 out of 23 patients (87%), while pre-treatment with glucose-insulin-potassium (group B) was associated with successful cardioversion in 17 out of 29 patients (58%), and no treatment (group C) in 19 out of 29 patients (65%) (P < 0.05 group A vs group B and group C).

#### Energy threshold for electrical conversion

The mean energy for electrical conversion in group B (103 ± 14 J . m⁻²) was significantly lower with respect to groups A (112 ± 11 J . m⁻²) and C (119 ± 10 J . m⁻²) (P < 0.01 group B vs groups A and C).

#### Changes in clinical characteristics after cardioversion

Immediately following successful cardioversion, no significant changes were observed in mean heart rate and arterial pressure between the three groups (Table 2). Sinus bradycardia (<50 beats . min⁻¹) occurred in two group A patients, four group B patients, and four group

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**Table 2 Heart rate and blood pressure in the three study groups**

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone</th>
<th>GIK</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>Heart rate (beats . min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study entry</td>
<td>115 ± 27</td>
<td>121 ± 15</td>
<td>128 ± 18</td>
</tr>
<tr>
<td>Pre-DCC</td>
<td>78 ± 8*</td>
<td>72 ± 8*</td>
<td>74 ± 6*</td>
</tr>
<tr>
<td>Post DCC</td>
<td>68 ± 6*</td>
<td>66 ± 5*</td>
<td>64 ± 4*</td>
</tr>
<tr>
<td>24 h</td>
<td>71 ± 9*</td>
<td>67 ± 7*</td>
<td>68 ± 9*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study entry</td>
<td>125 ± 7</td>
<td>130 ± 9</td>
<td>130 ± 10</td>
</tr>
<tr>
<td>Pre-DCC</td>
<td>125 ± 10*</td>
<td>130 ± 10</td>
<td>125 ± 5</td>
</tr>
<tr>
<td>Post DCC</td>
<td>115 ± 5</td>
<td>120 ± 10</td>
<td>120 ± 5</td>
</tr>
<tr>
<td>24 h</td>
<td>117 ± 11</td>
<td>124 ± 15</td>
<td>124 ± 9</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study entry</td>
<td>85 ± 5</td>
<td>90 ± 8</td>
<td>90 ± 7</td>
</tr>
<tr>
<td>Pre-DCC</td>
<td>85 ± 5</td>
<td>90 ± 8</td>
<td>80 ± 5</td>
</tr>
<tr>
<td>Post DCC</td>
<td>88 ± 7</td>
<td>84 ± 4</td>
<td>85 ± 7</td>
</tr>
<tr>
<td>24 h</td>
<td>80 ± 5</td>
<td>78 ± 10</td>
<td>68 ± 11</td>
</tr>
</tbody>
</table>

Mean ± SD. DCC=direct-current conversion; 24 h=24 h after DCC. *P < 0.05 vs study entry. For the other abbreviations, please refer to Table 1.
C patients, but in all cases it was well tolerated and short-lasting (<30 s): no sino-atrial blocks, atrioventricular blocks or ventricular arrhythmias occurred in any of the three groups.

Recurrences of atrial fibrillation
At 24 h after cardioversion the rate of early recurrences was very low and similar in the three groups: A, n=1 (5%); B, n=1 (5%); C, n=2 (10%) (P=ns). At hospital discharge no significant modifications in mean heart rate and systolic/diastolic blood pressures were observed (Table 2). At 2 months' follow-up the rate of relapses was lower in group A (n=6; 31%) with respect to groups B (n=9; 56%) and C (n=10; 52%) (P<0·01) (Fig. 2).

Side-effects
No drops-out and no side-effects were reported during the study before conversion or during the follow-up. In particular no significant changes in thyroid function were reported in group A patients with respect to baseline or pre-direct-current conversion periods: FT₃, 3·5±0·3; FT₄, 9·3±0·7; TSH 3·4±5 (P=ns).

Discussion
In patients with persistent atrial fibrillation electrical conversion has been proposed as the gold-standard therapy to restore sinus rhythm[11–3]. However, in older patients (>57 years of age), with long-term atrial fibrillation (>3 months), even in the presence of preserved exercise tolerance (New York Heart Association functional class I–II), several electrical conversion attempts with concomitant antiarrhythmic therapy are often necessary because of the low success rate and the high incidence of early recurrence of atrial fibrillation[4–6]. Recent experimental studies have provided electrophysiological bases of this phenomenon. It has been hypothesized that long-term atrial fibrillation with chronic rapid atrial rates induces electrical remodelling of the atria, characterized by a progressive decrease in atrial refractoriness, and loss of rate-related shortening of the effective refractory period[10,11]. Although not yet demonstrated, it can be speculated that a decrease in intracellular potassium develops, mediated by an adenosine triphosphate depletion on adenosine triphosphate-sensitive potassium channels[20–22].

Figure 2 Cox survival graph comparing the percentage of patients in sinus rhythm after successful direct-current cardioversion (DCC) at 1 day and 2 months follow-up among the three groups: □=amiodarone; ●=glucose–insulin–potassium; ▲=control.
decreased the action potential duration at 90% repolarization in guinea-pig atrial muscle, but no data are available in a human study[32].

Influence of amiodarone on electrical conversion effectiveness

The results of this study indicate that in patients with persistent atrial fibrillation, electrical conversion plus amiodarone pre-treatment is a safe and effective procedure and allows restoration of sinus rhythm in almost 90% of patients. In addition, amiodarone treatment does not increase the energy necessary for the conversion of persistent atrial fibrillation, in agreement with previous non-controlled reports[33]. It maintains the ventricular rate under control before electrical conversion, similarly to diltiazem therapy.

Preliminary data from uncontrolled or non-randomized studies have described the efficacy and safety of combined electrical conversion and amiodarone therapy, especially in the setting of atrial fibrillation resistant to electrical and/or chemical conversions. In a non-randomized study, Sagrista-Sauleda et al. analysed the role of amiodarone administration on the effectiveness and complications of electrical cardioversion of atrial fibrillation: the pre-treatment with amiodarone increased, but not significantly, the effectiveness of electrical conversion on sinus rhythm restoration[29]. The discrepancy with our findings may be related to the fact that Sagrista-Sauleda et al. studied a non-homogeneous population (also affected by atrial flutter or atrial tachycardia) and with a wide range of atrial fibrillation duration (<12 weeks in 64% of patients). As a consequence, in their control group the electrical conversion procedure had a high success rate, which may have affected their results. Moreover, amiodarone reduced the energy threshold for effective electrical conversion, but this reduction was not statistically significant[29].

More recently Opolski et al.[30] evaluated, in a small group of atrial fibrillation patients (n=49), the effectiveness of pre-treatment with oral amiodarone: electrical conversion allowed the return of sinus rhythm in only 59% of the patients but this population was characterized by persistent atrial fibrillation, unresponsive to several previous treatments. However, in this study also no significant complications were related to the amiodarone therapy.

Sinus rhythm conversion during amiodarone therapy

In our study, a spontaneous conversion to sinus rhythm during amiodarone pre-treatment was achieved in 25% of the patients: this finding agrees with the 18% of pre-electrical sinus rhythm conversion observed by Opolski et al.[30]. In other studies, 16 to 71% of patients with persistent atrial fibrillation converted to sinus rhythm during oral amiodarone loading[12-19]. This phenomenon has recently been confirmed by Tielman et al. who studied factors determining conversion of difficult-to-treat atrial fibrillation by oral amiodarone (30 days, 600 mg daily)[31]. At the end of the pre-treatment phase, before the electrical conversion period, 18% of the patients returned to sinus rhythm: the conversion rate was highly related to the desethylamiodarone plasma level, but also to arrhythmia duration, left atrial area, and concomitant treatment with verapamil.

Although in our population no thrombo-embolic events occurred and no embolic strokes were observed in the above-mentioned studies, the high rate of sinus rhythm conversion with amiodarone pre-treatment before electrical conversion in persistent atrial fibrillation could potentially increase the possibility of severe adverse events. Therefore an oral anticoagulant therapy, with maintenance of an international normalized ratio of 2.5-4.0, should be recommended before starting amiodarone therapy in persistent atrial fibrillation.

Influence of glucose–insulin–potassium infusion on electrical conversion and energy threshold

In contrast to previous hypotheses, pre-treatment with glucose–insulin–potassium did not improve the success rate of the electrical conversion procedure but only reduced the delivered energy during electrical conversion. The reduction in the electrical conversion threshold was probably mediated by a repolarizing effect of the potassium on the atrial cells and consequently a physiological response to external shock was obtained.

Moreover, the effect of potassium infusion may have been very limited because we infused the glucose–insulin–potassium solution for only 24 h: a significant beneficial effect may be obtained by longer administration of the solution. However, recent studies did not find any effect of the adenosine triphosphate-dependent potassium channel blocker glibenclamide on atrial fibrillation-induced electrical remodelling of the atria[34,35].

Early recurrence of atrial fibrillation

No controlled data are available on early (<24 h) recurrence after the electrical conversion procedure. Only Bianconi et al.[36] evaluated the effect of a class IC drug (propafenone) administered 48 h before electrical conversion on early relapse (24 and 48 h after): the early recurrence was significantly lower in the propafenone group with respect to the control group both at 24 h (29% vs 5%) and at 48 h (36% vs 12%). However, several warnings have been raised concerning the clinical use of class IC drugs[37,38].
Our study is the first controlled trial investigating the effect of a class III drug on early relapse (<24 h): in the overall population a low incidence was observed, similar to the effect of a class IC drug[36]. In the group A patients, it is possible to hypothesize the beneficial effect of amiodarone either on the prolongation of the atrial refractoriness and/or of the reduction in intracellular calcium concentration (calcium channel blocker effect of amiodarone)[37]. Both these mechanisms may have affected the atrial remodelling phenomenon.

However, there was also a similar low incidence of early recurrence in the control group (under diltiazem therapy). In experimental models, the atrial electrical remodelling has been associated with calcium-overload, mediated by opening of adenosine triphosphate-dependent potassium channels and antagonized by verapamil[41]. Concomitant administration of verapamil during amiodarone therapy appeared to be an independent factor determining the success of cardioversion[9]. Recently an uncontrolled study by Tieleman et al.[60] has suggested that calcium-lowering medications (verapamil, diltiazem and dihydropyridines) during atrial fibrillation can reduce early recurrence (1 week); however, in almost 50% of patients there was concomitant antiarrhythmic therapy which may have affected the results.

Although not supported by experimental data, it is also possible that diltiazem, like verapamil, can reduce the incidence of early recurrence of atrial fibrillation by attenuating the rate-induced electrical remodelling. This conclusion cannot be established from the data of our study: our investigation was not focused on the determination of the possible beneficial effect of diltiazem, and lacked a true-untreated control group.

**Follow-up**

Several studies have investigated the efficacy of amiodarone in maintaining sinus rhythm in the setting of populations with cardiac diseases[7–12]. However, the majority of these investigations were not randomized and amiodarone was employed as a last resort drug, in difficult-to-treat atrial fibrillation patients, i.e. refractory to other antiarrhythmic agents. Low-dose amiodarone was successful in maintaining sinus rhythm in 53–79% of patients during a mean follow-up of 15–27 months[12–19].

In our controlled randomized trial, 2 months after direct-current conversion, low-dose amiodarone therapy maintained sinus rhythm in 70% of the study population: this finding is in agreement with previous reports. Gosselink et al. administered low-dose amiodarone (204 ± 66 mg . day⁻¹) to 89 patients with persistent atrial fibrillation following electrical conversion[17].

Sinus rhythm maintenance was 68% at 3 months and 61% at 1 year, with the highest incidence of recurrence during the first 2 months. Another large retrospective study by Chun et al.[80] reported that the percentage of patients with persistent atrial fibrillation remaining in sinus rhythm after electrical conversion was 87%, 70% and 55% at 1, 3 and 5 years, respectively; however these authors did not provide the early recurrence data.

Furthermore our results suggest that the calcium channel blocker therapy (diltiazem), even if started 4 weeks before electrical conversion, compared to amiodarone, may have no significant effect on long-term sinus rhythm maintenance. This observation, together with the experimental data showing that the atrial electrical remodelling is completely reversible within 1 week after sinus rhythm restoration[11], suggests that mechanisms involved in long-term atrial fibrillation recurrences are different from those involved in the short-term recurrences.

**Limitation of the study**

The external electrical conversion used in this study is not the most appropriate method to evaluate the exact energy requirement for atrial cardioversion. However, this method is non-invasive, currently used in clinical practice; in addition we used the same protocol in all patient groups, making the results comparable.

The overall success rate of the electrical cardioversion in the control groups is low; this could not be attributed to the very gradual build up of shocks because this protocol was used in all groups, but it may be due to the relatively long past history of arrhythmia in our study population.

**Conclusions**

In an out-of-hospital population with persistent atrial fibrillation pre-treatment with amiodarone allows (i) ventricular rate control similar to diltiazem therapy, (ii) a high percentage of spontaneous sinus rhythm conversion, reducing the electrical conversion requirement, (iii) improvement in electrical conversion procedure efficacy without affecting the defibrillation threshold, (iv) early reduction of recurrence, similar to calcium channel blocker therapy, and (v) reduction in the incidence of late atrial fibrillation recurrence (at the 2 month follow-up). These benefits have been reached without significant adverse events.

On the basis of the above findings, amiodarone pre-treatment may be considered for the treatment of out-of-hospital patients with persistent atrial fibrillation waiting for electrical conversion procedure.

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