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# Original articles

## Variables correlated with early relapses after external electrical cardioversion of persistent atrial fibrillation

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**Key words:**  
Atrial fibrillation;  
Cardioversion.

**Background.** The aim of this study was to identify the clinical and echocardiographic variables possibly correlated with the early relapses of atrial fibrillation (AF) after external electrical cardioversion (EC) in a large cohort of patients with persistent AF.

**Methods.** Two hundred patients (117 males, 83 females, mean age  $67.9 \pm 8.7$  years) with successful EC of persistent AF ( $> 72$  hours) were included in the present study. In order to identify the predictors of early relapses (within 7 days) of AF, 16 clinical and echocardiographic variables were compared at univariate analysis. The variables with a  $p$  value  $< 0.10$  at univariate analysis were subsequently analyzed at multivariate analysis.

**Results.** Seventy-five patients (37.5%) had relapses of AF within 7 days of EC. By univariate analysis only a younger age ( $65.9 \pm 8.9$  vs  $69.0 \pm 8.3$  years,  $p = 0.01$ ) was found to be significantly correlated with a higher incidence of early relapses of AF. At multivariate analysis no variable was found to be significantly correlated with early relapses of AF.

**Conclusions.** In patients with persistent AF, recurrences of this arrhythmia within 7 days of EC occur frequently (37.5%). Multivariate analysis did not reveal any clinical or echocardiographic variable significantly correlated with the early recurrence of AF.

(Ital Heart J 2003; 4 (8): 532-536)

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Received January 10, 2003; revision received May 20, 2003; accepted June 13, 2003.

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### Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias, with a prevalence that increases in patients  $> 60$  years old<sup>1-4</sup>. Over time, it tends to become persistent or chronic, even if no underlying structural heart disease is present<sup>3,4</sup>. Moreover, it is a dangerous arrhythmia; the risk of thromboembolic events in patients with chronic non-rheumatic AF is up to 5 times higher than in those in sinus rhythm<sup>5</sup>; stroke volume and cardiac output are decreased by up to 35%, and cardiopulmonary exercise capacity is reduced<sup>6,7</sup>. Therefore, in some subgroups of patients an attempt should be made to restore sinus rhythm. However, the spontaneous or pharmacological interruption of the arrhythmia is very rare in cases of long-lasting AF<sup>8,9</sup>. External electrical cardioversion (EC) is usually necessary to restore sinus rhythm, and it is successful in 70-90% of patients<sup>10-12</sup>.

Few data on the incidence of early relapses (within the first days) after external EC of persistent AF are available<sup>11-17</sup>. More-

over, little is known about the clinical and electrophysiological determinants of early relapses, although there are some indications that an intracellular calcium overload may play an important role<sup>13</sup>.

The aim of this study was to analyze the clinical and echocardiographic variables that may be correlated with early relapses of AF after external EC in a large cohort of patients with persistent AF.

### Methods

**Patients.** Two hundred and thirty patients referred to our Institution for elective EC of persistent AF were enrolled in the present study ( $> 72$  hours).

**Electrical cardioversion.** On inclusion in the waiting list for elective EC, each patient's clinical and pharmacological history was collected, and physical examination, ECG, and echocardiography were performed. All patients received oral anticoagulants for at least 4 weeks before and 4 weeks after EC.

All patients gave their written informed consent to take part in the study.

External EC was performed under general anesthesia with intravenous propofol or tiopentale in fasting patients. Shocks were delivered by means of external paddles placed in the anterior-apex position and connected to an external cardioverter (CardioServ, Hellige Inc., Freiburg, Germany). The energy delivered initially varied from 200 to 300 J according to the patient's body mass index. If the first attempt at cardioversion failed, another shock was delivered in the antero-posterior position at 360 J.

EC was deemed successful if at least two consecutive sinus beats were recorded immediately after the shock.

**Echocardiographic analysis.** Transthoracic two-dimensional imaging and pulsed wave 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, USA) before the termination of AF. The left ventricular ejection fraction was determined by calculating the end-diastolic and end-systolic volumes as described by Folland et al.<sup>18</sup>. The left atrial size was measured at end-systole in the parasternal long-axis view.

**Follow-up.** After cardioversion, the cardiac rhythm was continuously monitored for 5 min. Thereafter, ECG was performed after 6 hours and after 7 days. For the purposes of this study, the reappearance of AF within 5 min was defined as a recurrence, even if cardioversion repeated during the same procedure resulted in a sustained sinus rhythm.

Only the ECG-documented reappearance of AF was considered as a recurrence.

Immediate relapse was defined as the reappearance of AF within 5 min of EC. Early relapse was defined as the reappearance of AF within 7 days of EC.

The patients were invited to continue the same therapy for at least 1 month after EC.

**Statistical analysis.** Continuous variables are presented as mean  $\pm$  SD. Discrete variables are presented as percentages.

For the patients with successful EC, 16 clinical and echocardiographic variables were evaluated at univariate analysis in order to identify the significant and independent predictors of the early relapse of AF. Univariate comparisons between variables were made using the Fisher's exact test or  $\chi^2$  test for categorical variables and the unpaired Student's t-test for continuous variables. Variables with a p value  $<$  0.10 in the univariate model were subsequently evaluated at multivariate analysis with a logistic regression model using the backward stepwise method according to Wald<sup>19</sup>. The variables in the initial model included: 1) sex, 2) age, 3) number of previous AF relapses, 4) duration of

the last episode of AF, 5) presence of structural heart disease, 6) left atrial size, 7) left ventricular end-diastolic diameter, 8) left ventricular ejection fraction, 9) pretreatment with intracellular calcium-lowering drugs, 10) pretreatment with verapamil, 11) pretreatment with intracellular calcium-lowering drugs other than verapamil (other calcium antagonists, and all beta-blockers apart from sotalol), 12) pretreatment with digoxin, 13) pretreatment with antiarrhythmic drugs (amiodarone, sotalol, class IC drugs), 14) pretreatment with amiodarone, 15) pretreatment with class IC drugs, and 16) pretreatment with sotalol. We considered that there was a significant increase in risk if the 95% confidence intervals exceeded 1 and the p value at the Wald test was  $<$  0.05.

Analysis was performed using SPSS (version 6.1.3, Chicago, IL, USA) software.

## Results

All external EC were performed without complications.

Sinus rhythm was restored in 200/230 patients (87%). The clinical and echocardiographic characteristics of the 200 patients with successful EC are shown in table I. With regard to antiarrhythmic therapy, 140/200 patients (70%) were receiving antiarrhythmic drugs (amiodarone, sotalol or class IC drugs). Among these, 14/140 patients (10%) were on a combined antiarrhythmic therapeutic regimen.

There were 11/200 (5.5%) immediate and 75/200 (37.5%) early relapses of AF.

Univariate analysis (Table II) revealed that only a younger age was independently correlated with the early relapse of AF ( $65.9 \pm 8.9$  years for early relapses vs

**Table I.** Clinical and echocardiographic characteristics of the study population.

Age (years)	67.9 $\pm$ 8.7
Male (%)	59
Heart disease (%)	71
Relapses of AF (n=)	2.0 $\pm$ 7.2
AF duration (days)	93.5 $\pm$ 116.7
Left atrial size (mm)	46.6 $\pm$ 6.1
LVEDD (mm)	54.9 $\pm$ 35.8
LVEF (%)	56.4 $\pm$ 9.1
Drugs* (%)	
Amiodarone	62
Sotalol	4
Class IC	11
Digoxin	46
Ca <sup>2+</sup> -lowering	47
Ca <sup>2+</sup> -lowering other than verapamil	24
Verapamil	23

AF = atrial fibrillation; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction. \* more than one per patient possible.

**Table II.** Univariate predictors of early relapses of atrial fibrillation (AF).

Variables	AF (n=75)	No AF (n=125)	p
Males (%)	54.7	60.8	0.48
Age (years)	65.9 ± 8.9	69.0 ± 8.3	0.01
No. previous AF relapse	2.8 ± 11.5	1.5 ± 2.0	0.23
Duration of the last episode of AF (days)	90.0 ± 90.6	95.6 ± 130.1	0.74
Presence of structural heart disease (%)	69.3	71.2	0.90
Left atrial size (mm)	47.9 ± 6.1	46.4 ± 6.1	0.10
LVEDD (mm)	53.0 ± 5.7	52.1 ± 5.4	0.24
LVEF (%)	55.9 ± 10.1	56.7 ± 8.4	0.24
Pretreatment (%)			
Amiodarone	56.0	65.6	0.23
Sotalol	6.7	1.6	0.14
IC drugs	12.0	10.4	0.91
Digoxin	42.7	48.0	0.56
Ca <sup>2+</sup> -lowering drugs	50.7	44.8	0.51
Ca <sup>2+</sup> -lowering drugs other than verapamil	22.7	24.8	0.86
Verapamil	26.7	20.0	0.18
Antiarrhythmic drugs	65.3	68.0	0.82

LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction.

69.0 ± 8.3 years for no early relapses, p = 0.01). At multivariate analysis, no variable was found to be significantly correlated with early relapses of AF.

In particular, the percentages of patients who were pretreated with calcium-lowering drugs were similar between patients who had an early relapse of AF and those who did not (50.7% of patients with an early relapse vs 44.8% of those without, p = 0.51).

## Discussion

The main findings of this study were that 1) early relapses are frequent after external EC (37.5%) of persistent AF, and 2) at multivariate analysis no clinical or echocardiographic variable was found to be significantly correlated with the early recurrence of AF.

**Previous studies.** The clinical importance of the early relapse of AF after external or internal shock has only recently been emphasized<sup>12-17,20-24</sup>. This importance has been recognized after the introduction of the implantable device for the treatment of AF<sup>24</sup>: patients in whom these devices were implanted were unable to tolerate the repetition of shocks for the relapse of AF within hours or days of a successful shock<sup>23</sup>. However, it soon became clear that the early relapse of AF was a clinically important event even when occurring after the delivery of an external shock. Tieleman et al.<sup>13</sup> reported an impressive incidence (36%) of AF relapses within 5 days of a successful external EC. This means that more than one third of patients undergo a useless cardioversion despite a successful shock. To date, only a few authors investigated the incidence of early AF relapses after external EC (Table III)<sup>11-17</sup>. Most of these authors

**Table III.** Rates of immediate and early recurrences (ER) after external electrical cardioversion of atrial fibrillation: findings from previous studies.

Authors	No. patients	ER (%)	Timing of ER
Bianconi et al. <sup>11</sup>	96	18	24 hours
Bertaglia et al. <sup>12</sup>	90	28	7 days
Tieleman et al. <sup>13</sup>	61	36	5 days
Yu et al. <sup>14</sup>	50	26	1 min
De Simone et al. <sup>15</sup>	107	14	7 days
Daoud et al. <sup>16</sup>	337	9	5 min
Villani et al. <sup>17</sup>	115	7	24 hours

dealt with the relapse of AF occurring immediately after the shock, i.e. within the first 24 hours<sup>11,14,16,17</sup>. Those who reported about the true early recurrences<sup>12,15</sup> found a lower incidence of AF relapses than that obtained by Tieleman et al.<sup>13</sup>. However, all these studies enrolled only a few patients and none investigated the possible predictors of the early relapse of AF.

**Present study.** Our data may be considered as an extension of those of the aforementioned studies. We present a broader and potentially clinically relevant analysis of early relapses after external EC of persistent AF. From the patient's perspective, the relapse of AF not only after a few minutes but also after a few days following an EC is equivalent to a complete failure. Patients who undergo an EC should be informed that the procedure could fail not only owing to the impossibility of interrupting the arrhythmia, but also and more frequently because of the occurrence of early relapses.

We tried to identify an association between several clinical and echocardiographic variables and the occur-

rence of early relapses. The only variable that at univariate analysis correlated with the occurrence of early relapses was a younger age. However, this result was not confirmed at multivariate analysis.

**Effects of intracellular calcium-lowering drugs.** Recently, the term atrial electrical remodeling was introduced by Wijffels et al.<sup>25</sup> to indicate the significant shortening of the atrial refractory period and the reversal of the physiological rate adaptation of the atrial refractory periods that appeared after 2-4 weeks of artificially maintained AF. This phenomenon has been claimed to be responsible for the high incidence of early recurrences of AF<sup>13</sup>. Intracellular calcium-lowering drugs such as verapamil have been reported to be efficacious in preventing atrial electrical remodeling after rapid atrial pacing or spontaneous AF of short duration<sup>26,27</sup>. Their usefulness in preventing this phenomenon after long-lasting episodes of AF is still subject of debate<sup>13,15,17,28-32</sup>. Our data did not demonstrate any associations between pretreatment with verapamil or other intracellular calcium-lowering drugs and a reduced incidence of early relapses of AF (Table III). There are some possible explanations for the different effects of verapamil on the prevention of AF-induced electrical remodeling after brief or long-lasting episodes of spontaneous or induced AF. First, pretreatment with intracellular calcium-lowering drugs may prevent the cytosolic calcium overload related to the ionic mechanisms that account for the electrical remodeling occurring during the first hours of AF. However, after weeks or months of AF, changes in the gene expression of the calcium-handling proteins and intracellular structural modifications further contribute to the cytosolic calcium overload, in a manner that cannot be modified by pretreatment with verapamil<sup>33</sup>. Second, it could be that verapamil exerts beneficial effects only when it is taken during sinus rhythm, but not after the beginning of AF<sup>34</sup>.

**Clinical implications.** The findings of the present study confirm that the incidence of early recurrences after external EC of persistent AF is very high (37.5%). These results highlight the need to discuss this possible outcome with the patient before submitting him to EC. The patient should be informed of the possibility that AF could relapse quickly.

Unfortunately, those patients who are at high risk for the early relapse of AF cannot be identified on a clinical and echocardiographic basis.

Pretreatment with intracellular calcium-lowering drugs started after the beginning of the arrhythmia does not seem to reduce the occurrence of early AF relapse.

**Study limitations.** It is difficult to correctly define the very first beats after the shock without an endocardial lead. Thus, a successful EC with the reinitiation of AF after a few sinus beats may be mistakenly considered as

an unsuccessful EC. However, in view of the high rate of successful external EC observed in our series (87%) we believe that our results have not been influenced by this potential bias.

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