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Electrophysiology

Pretreatment With Verapamil in Patients With Persistent or Chronic Atrial Fibrillation Who Underwent Electrical Cardioversion

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OBJECTIVES To evaluate, in a prospective and randomized fashion, the efficacy of a pretreatment with verapamil (V) in reducing recurrences of atrial fibrillation (AF) after electrical cardioversion (C).

BACKGROUND The increased vulnerability for AF recurrence is probably due to AF-induced changes in the electrophysiologic properties of the atria. This electrical remodeling seems to be due to intracellular calcium overload.

METHODS One hundred seven patients with persistent or chronic AF underwent external and/or internal C. All patients received oral propafenone (P) (900 mg/day) three days before and during the entire period of follow-up (three months). In the first group, patients received only the P. In the second group, in adjunct to P, oral V (240 mg/day) was initiated three days before C and continued during the follow-up. Finally, in the third group, oral V was administered three days before and continued only for three days after electrical C.

RESULTS During the three months of follow-up, 23 patients (23.7%) had AF recurrence. Mantel-Haenszel cumulative chi-square reached a significant level only when comparing AF free survival curves of group I versus group II and group III (chi-square = 5.2 and 4, respectively; $p < 0.05$). Significantly, 15 (65.2%) AF relapses occurred during the first week after cardioversion with a higher incidence in group I (10/33 patients, 30.3%) than group II (2/34 patients, 5.9%; $p = 0.01$) and group III (3/30 patients, 10%; $p = 0.04$).

CONCLUSIONS Six days of oral V administration centered on the C day, combined with P, significantly reduce the incidence of early recurrences of AF compared with P alone. (J Am Coll Cardiol 1999;34:810–4) © 1999 by the American College of Cardiology

In patients with atrial fibrillation (AF), long-term maintenance of sinus rhythm after successful cardioversion is difficult, mainly because of a high recurrence rate of AF within the first month after cardioversion. Recent studies suggest that an increased vulnerability to AF recurrence is probably due to AF-induced changes in the electrophysiologic properties of the atria (1–2). This electrical remodeling, which has been seen to be completely reversible in goats within one week after restoration of sinus rhythm (1), seems to be due to intracellular calcium overload. Administration of calcium gluconate during rapid atrial pacing in dogs induced a distinct delay in recovery from electrical remodeling after cessation of pacing (3), while verapamil infusion during rapid atrial pacing (3,4) or short episodes of induced AF (5,6) significantly reduced the electrical remodeling of the atria. To date, only one retrospective study (7) has evaluated the role of intracellular calcium-lowering drugs in the clinical setting. The aim of our study was to evaluate in a prospective and randomized fashion the efficacy of a pretreatment with verapamil in reducing recurrences of AF in patients with persistent or chronic AF after external or internal electrical cardioversion.

METHODS

Patient population. One hundred seven out of 134 consecutive patients with persistent or chronic AF (8), referred to our centers for electrical cardioversion, were enrolled. Exclusion criteria were: 1) a previous history of sick sinus syndrome and/or trifascicular block; 2) mean daytime ventricular rate of 60 beats/min and/or 3 s pause during 24-h

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Abbreviations and Acronyms
AF = atrial fibrillation
ECG = electrocardiogram

electrocardiogram (ECG) Holter recording; 3) a previous history of a sustained ventricular arrhythmia, cardiac arrest or congenital QT syndrome; 4) AF due to reversible causes (e.g., hyperthyroidism); 5) a history of myocardial infarction or a revascularization procedure within the previous six months; 6) a history of thromboembolic events; 7) a left atrial thrombus diagnosed by transesophageal echocardiography obtained the day before cardioversion; 8) major hepatic or renal dysfunction; 9) signs of severe cardiac or respiratory insufficiency with a left ventricle ejection fraction 35%; 10) an implanted pacing device.

Study protocol. All patients gave informed written consent to take part in the study. A detailed clinical examination, thyroid function tests, chest radiography and transthoracic and transesophageal echocardiography were routinely performed. Calcium channel blockers, beta-adrenergic antagonists and all antiarrhythmic agents, including digitalis or other drugs depressing atrioventricular node conduction, were stopped for at least five half-lives and for at least two months in the case of amiodarone before randomization. All patients were treated with oral anticoagulation using warfarin sodium to achieve an international normalized ratio of 2.5 to 3.5 for three weeks before electrical cardioversion. Three days before cardioversion, patients were randomized into three groups. All patients received oral propafenone (900 mg/day) three days before and during the entire period of follow-up. In the first group, patients received only the oral propafenone. In the second group, as in adjunct to propafenone, oral verapamil (240 mg/day) was initiated three days before electrical cardioversion and both were continued during the follow-up; finally, in the third group, oral verapamil (240 mg/day) was administered three days before and continued for three days after electrical cardioversion. All patients were followed up for three months. Clinical examination and 12-lead ECG were scheduled every day during the three days of hospitalization after cardioversion and, after hospital discharge, at 1 week, 30 and 90 days.

Electrical cardioversion. During continuous 12-lead ECG monitoring and heavy sedation with propofol (2 mg/kg), up to three synchronized external monophasic shocks (200, 360, 360 J) were delivered to restore sinus rhythm. A successful cardioversion was defined as a cardioversion that restored sinus rhythm for at least three beats. An AF recurrence, after this period, was classified as an early recurrence on the first day. Patients in whom an initial attempt of external cardioversion was ineffective, or who had previously undergone external cardioversion without success, underwent internal atrial defibrillation. In these patients two quadripolar catheters for pacing, sensing and defibrillation were located in the lateral right atrium and left pulmonary vein. After sedation with diazepam (10 mg IV [intravenous]) or heavy sedation with propofol (2 mg/kg), and during continuous ECG monitoring, shocks were delivered with a step-up (5, 10, 15, 30 J) protocol until sinus rhythm was restored. Thereafter, cardiac rhythm was monitored by telemetry for at least 4 h and a 12-lead ECG was performed at 12, 24 and 36 h after electrical cardioversion. Patients were generally discharged 36 to 48 h after cardioversion.

Statistical analysis. Continuous variables are expressed as mean ± standard deviation. The Fisher exact test was used to compare proportions. Atrial fibrillation-free survival data from the three groups were analyzed by the Mantel-Haenszel cumulative chi-square test. Clinical data from the three study groups were compared using a Student *t* test with Bonferroni correction for multiple comparisons.

RESULTS

Patient characteristics. There was no significant difference in any clinical characteristics among the three groups, as summarized in Table 1. The duration of AF was at least of two months. In seven (6.5%) patients, sinus rhythm was documented at the time of cardioversion (one in group I, three in group II and three in group III). There was no difference in the incidence of sinus rhythm restoration between patients receiving propafenone alone or combined with verapamil (2.9% vs. 8.2%, p = NS). Eight (8%) patients were dropped from the follow-up because of pharmacological side effects (Table 2). However, only the three patients who stopped the pharmacological therapy before cardioversion were not enrolled. There was no difference in the incidence of complications between patients who received propafenone alone or combined with verapamil (5.9% vs. 8.2%, p = NS). Of the remaining 97 patients who entered follow-up, 33 were randomized in the group I, 34 in group II and 30 in group III.

Electrical cardioversion. All patients successfully underwent electrical cardioversion. In 53 out of 67 (79%) patients, external cardioversion restored sinus rhythm with a mean of 2.0 ± 0.8 shocks and a mean cumulative energy of 567 ± 304 J. In 44/44 (100%) patients, successful internal cardioversion was performed with a mean of 2.0 ± 0.9 shocks at a mean energy of 10.8 ± 6.4 J.

AF recurrences. During the three months of follow-up, 23 patients (23.7%) had AF recurrence. No patients developed atrial flutter during the follow-up. Figure 1 shows AF-free survival during the follow-up period of each group. Mantel-Haenszel cumulative chi-square among the three curves reached a significant level when comparing group I with groups II and III (chi-square = 5.2 and 4, respectively; $p < 0.05$), but not when comparing group II with group III. Significantly, 15 (65.2%) AF relapses occurred during the first week after cardioversion with a higher incidence in

Table 1. Clinical Characteristics

	Group I (34)	Group II (38)	Group III (35)	p
Age (yrs)	63.7 ± 10	62.9 ± 10.5	63.8 ± 11.4	NS
Gender (M/F)	20/14	23/15	21/14	NS
LA diameter (mm)	45.8 ± 6.6	45.6 ± 5.9	45.8 ± 6.2	NS
LVEF (%)	49.1 ± 9.3	49.8 ± 8.6	49.5 ± 9.2	NS
Duration AF (months)	17.4 ± 20.8	17.1 ± 22	16.5 ± 21.9	NS
Previous AF episodes	4.9 ± 2.7	4.8 ± 2.6	4.5 ± 2.2	NS
Previous AA drugs	3.2 ± 0.9	3.1 ± 0.8	3.3 ± 1	NS
Heart disease				NS
None	4	5	3	NS
Hypertension	17	19	17	NS
CHD	7	7	8	NS
Valvular	4	5	6	NS
DCM	2	2	1	NS

AA = antiarrhythmic; CHD = coronary heart disease; DCM = dilated cardiomyopathy; LA = left atrium; LVEF = left ventricular ejection fraction.

group I (10/33 patients, 30.3%) than in groups II (2/34 patients, 5.9%; p = 0.01) and III (3/30 patients, 10%; p = 0.04). The remaining eight relapses were distributed among the three groups without significant statistical difference (three in group I, three in group II and two in group III). The overall incidence of AF recurrences was higher in group I than in group II (13 vs. 5, p = 0.02) and group III (13 vs. 5, p = 0.04), whereas there was no difference between group II and III. All but two episodes of AF recurrences were persistent and required a new electrical cardioversion; in one patient in group I and one in group II, the AF relapse lasted 8 and 24 h, respectively.

DISCUSSION

To our knowledge, this is the first study to demonstrate, in a prospective and randomized fashion, the efficacy of an oral pretreatment with verapamil, associated with propafenone, in reducing early recurrences of AF after external or internal electrical cardioversion. The time course of AF relapses, with 68.4% of overall AF recurrence within seven days, confirms that recovery from electrical remodeling of the atria occurs within few days, and might explain why the reduction of early AF recurrences resulted in overall AF recurrence reduction.

Electrical remodeling of the atria. The clinical observations that paroxysmal AF can progress to chronic AF (9) and that the incidence of successful restoration and maintenance of sinus rhythm is higher in patients with recent-onset AF (10) have suggested that AF might be self-perpetuating. Recently, several invasive studies, performed both in animals and in humans (1–6,11,12), have shown that AF begets AF, and that this is due to an electrical remodeling of the atria, which consists of shortening of atrial refractory periods, loss of the physiologic rate-dependent adaptation of the refractory period and short duration of monophasic potential. Although the exact mechanisms by which these electrophysiologic changes occur are largely unknown, reduction of the electrical remodeling process might prevent or diminish the negative effects of the duration of AF on the success rate of

Table 2. Complications

Patient No.	Group	Side Effect	Time
4	III	Bradycardia	36 h after R, before CV
11	I	Bradycardia	1 h after CV
15	III	Bradycardia	60 h after R, before CV
41	II	II degree AV block	168 h after CV
57	II	Low pressure	36 h after R, before CV
74	I	I degree AV block	6 h after CV
97	III	II degree AV block	24 h after CV
106	II	Bradycardia	120 h after CV

CV = cardioversion; R = randomization and pretreatment beginning.

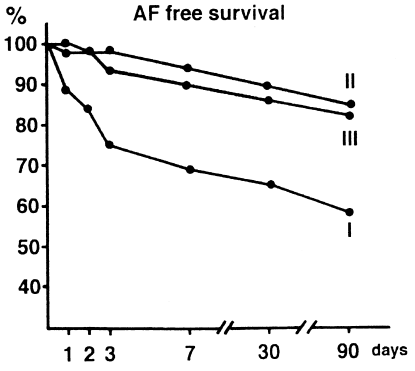

Figure 1. AF-free survival data during follow-up period of each group. Mantel-Haenszel cumulative chi-square among the three curves reached a significant level when comparing group I with group II and III (chi-square = 5.2 and 4, respectively; p < 0.05), but not when comparing group II with group III.

cardioversion and might reduce early AF recurrences after successful cardioversion. In our study, most AF recurrences (68.4%) occurred in the first week after cardioversion, while the remaining ones were progressively less frequent during the three-month follow-up period (Fig. 1). A period of seven days might be the clinical representation of recovery from electrical remodeling of the atria in patients with AF lasting at least two months. Our data are in agreement with Tielman et al. (7), who analyzed the moment of recurrence of AF after successful electrical cardioversion with a time resolution of one day, and found a relatively high incidence of AF recurrences during the first five days after cardioversion. Moreover, in goats with pacing-induced chronic AF, Wijffels et al. (1) showed that electrical remodeling of the atria was completely reversible within one week after restoration of sinus rhythm. These data should focus our attention to reduce early recurrences of AF in order to reduce the overall incidence of AF recurrences.

Role of intracellular calcium-lowering drugs. Previous studies have shown that initiation of antiarrhythmic drugs before electrical cardioversion decreases the recurrence of AF (13–15). The finding that recovery from the electrical remodeling of the atria is critical in the restoration and maintenance of sinus rhythm suggests the use of drugs that could affect this recovering. Recent animal studies have suggested that intracellular calcium plays a pivotal role in the mechanism of the electrical remodeling of the atria (4,5). In goats, pacing-induced electrical remodeling was significantly reduced by the administration of verapamil during arrhythmia. As a result, after cessation of rapid atrial pacing, the atrial refractory period returned sooner to its control value (5). In contrast, rapid atrial pacing during hypercalcemia in dogs resulted in a distinct delay of recovery from electrical remodeling (4). Yu at al. (6) investigated the effect of atrial rate and antiarrhythmic drugs on the effective refractory period shortening induced by 10 min of tachycardia (fast atrial pacing and AF). They found that the atrial effective refractory period shortened after conversion of AF and that this shortening was attenuated after verapamil infusion but was unchanged after infusion of the other antiarrhythmic drugs (procainamide, propafenone, propanolol, *dl*-sotalol and amiodarone). In a retrospective analysis of 61 patients cardioverted for chronic AF, Tielman et al. (7) recently documented that the use of intracellular calcium-lowering drugs during AF was the only significant variable related to the maintenance of sinus rhythm after cardioversion ($p = 0.03$). To date, our study is the only one to compare, in a prospective and randomized fashion, a pretreatment with a class IC antiarrhythmic drug alone or combined with verapamil in patients undergoing electrical cardioversion. The higher incidence of AF recurrences in group I than in groups II and III (Fig. 1) confirms the data of Tielman et al. (7) and laboratory observations (4–6) suggesting that intracellular calcium-lowering drugs reduce electrical remodeling, which may in turn lead to a more rapid recovery from electrical remodeling after cardioversion. The lack of evidence of a higher efficacy of long-term therapy with verapamil (group II) compared with a short-term therapy (group III) supports the hypothesis that the recovery from electrical remodeling occurs in a few days and that after this period intracellular calcium-lowering drugs might have a marginal role in preventing AF recurrences.

Study limitations. The study has several potential limitations: 1) Although a faster recovery from electrical remodeling has been proposed as the mechanism by which calcium antagonists reduce early AF recurrences, the atrial effective refractory period has been measured only in some patients and we cannot assess whether calcium antagonists actually lengthen the atrial effective refractory period more than class IC antiarrhythmic drugs alone; 2) The moment of AF recurrence was documented at 1, 2, 3, 7, 30 and 90 days. Continuous telemetric ECG monitoring could better assess the exact time of AF relapses. However, previous studies (7) have already demonstrated a relatively high incidence of AF recurrences during the first five days after cardioversion; 3) The combined use of propafenone and verapamil, at a high dosage, raises the problem of the side effects. In our study eight (7.4%) patients were dropped because of pharmacologic side effects. However, because the verapamil regime, starting three days before and lasting three days after cardioversion, is undertaken by in-hospital patients, the clinical impact of side effects is probably reduced; 4) Although the results about AF recurrences were statistically significant, the number of patients included was small (about 30 per group). In a wider study, the difference in the rate of sinus rhythm restoration before cardioversion, complication, kind of AF recurrence (paroxysmal or persistent), number of previous episodes of AF, number of previous (failed) antiarrhythmic drugs used or any other clinical characteristics might reach a significant level.

Conclusions. The administration of oral verapamil combined with propafenone for six days, centered around the cardioversion day, significantly reduces the incidence of early AF recurrences compared with oral propafenone alone. The time course of AF relapses and the lack of benefits of long-term therapy with verapamil strongly support the hypothesis that calcium antagonists only facilitate recovery from electrical remodeling.

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