Can short-term verapamil therapy reduce the recurrence of atrial fibrillation after successful low energy intracardiac cardioversion?

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Atrial fibrillation; Cardioversion; Verapamil.

Background. **Calcium-lowering drugs seem to be able to reduce the recurrences of atrial fibrillation (AF) after cardioversion by preventing electrical remodeling of atrial cells. The aim of our study was to prospectively evaluate the efficacy of short-term verapamil therapy associated with propafenone or amiodarone in reducing recurrences of AF after low energy intracardiac cardioversion.**

Methods. **Eighty-two patients with chronic AF (mean duration 6.1 months, range 1-96 months) underwent low energy intracardiac cardioversion. Forty-one patients (Group A) were instructed to suspend antiarrhythmic therapy 48 hours before the procedure (only chronic amiodarone was allowed). The subsequent 41 patients (Group B), in addition to previous prescriptions, had to take verapamil (120 mg twice daily) for 3 days before low energy intracardiac cardioversion and for 7 days after cardioversion. A right atrium-coronary sinus or right atrium-left pulmonary artery electrode configuration was indifferently utilized. Propafenone (450-900 mg daily) or amiodarone (200 mg daily) was prescribed to all patients after cardioversion.**

Results. **Sinus rhythm was acutely restored in 80 patients (97.6%): the mean number of shocks delivered was 2.3 (range 1-5); the mean energy required was 10.5 J (range 7.2-19.8 J). No statistically significant differences were found between the right atrium-coronary sinus vs right atrium-left pulmonary artery electrode configuration regarding the energy required and the number of shocks delivered. Group A and Group B showed the same number of AF recurrences at the first month of follow-up.**

Conclusions. **In our study, short-term verapamil treatment associated with propafenone or amiodarone seems to be useless for the prevention of recurrent AF after low energy intracardiac cardioversion.**

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Introduction

Atrial fibrillation (AF) is a very common arrhythmia in clinical practice and, for several reasons, mainly the associated deleterious complications (stroke, thromboembolic events, heart failure, angina, etc.) and its relevant socio-economic impact (absence from work, psychological conditioning, drug costs, etc.) has generated new interest in recent years.

The cardiologist's most important clinical goals in the treatment of this arrhythmia are the restoration and maintenance of sinus rhythm as long as possible. When this becomes impossible, it is mandatory to achieve an adequate control of the ventricular rate and avoid thromboembolic accidents. Whenever AF is diagnosed and an attempt to restore sinus rhythm is indicated, this could be obtained pharmacologically, usually with class I or III antiarrhythmic drugs, or by electrical cardioversion. The latter can be performed by the external approach (transthoracic) or, in selected cases, by the internal approach (low energy intracardiac cardioversion).

Low energy intracardiac cardioversion has been introduced into clinical practice for the treatment of both acute and chronic AF[1-13]. With regard to the restoration of sinus rhythm, low energy intracardiac cardioversion is more efficacious than conventional external cardioversion[14-17].

The long-term success rate of pharmacological or electrical (external or internal) cardioversion is not satisfactory, considering that approximately only 50% of patients un-

dergoing a prophylactic antiarrhythmic therapeutic regimen remain in sinus rhythm at 1 year[18].

Relapses of AF are common (17-89%) during the first month after cardioversion and particularly during the first week[19,20]. Recent literature[21-23] reports that the early high recurrence rate of AF could be influenced by electrical remodeling which induces shortening of the atrial refractory period and causes an increased vulnerability to the reinduction of AF. Electrical remodeling seems to be completely reversible within 1 week after cardioversion and is possibly related to intracellular calcium overload[24-28]. Some authors[25,28] suggest that the use of intracellular calcium-lowering drugs might reduce electrical remodeling by decreasing intracellular calcium overload.

The aim of our study was to prospectively evaluate the efficacy of verapamil, a calcium channel blocker, associated with class IC or III conventional antiarrhythmic drugs, in avoiding recurrences in patients with chronic AF submitted to low energy intracardiac cardioversion.

Methods

Our study consisted of 82 consecutive patients (56 males, 26 females, mean age 62.8 years, range 25-78 years) who underwent low energy intracardiac cardioversion for chronic AF. Forty-two patients had systemic hypertension, 5 ischemic heart disease, 6 dilated cardiomyopathy and 10 mitral valve disease. Nineteen patients had no other signs of cardiac pathology except for AF (Table I). Patients were enrolled into the study if they met the following inclusion criteria: 1) a minimum duration of chronic AF (as documented at previous 12-lead ECG) lasting at least 1 month (mean 6.1 months, range 1-96 months), 2) informed consent to low energy intracardiac cardioversion as the preferred choice or as an alternative procedure to conventional external cardioversion. No specific exclusion criteria were applied in this series, except for overt congestive heart failure.

The 82 consecutive patients were divided into two groups: the first 41 patients (Group A) were instructed to withdraw oral therapy (antiarrhythmic drugs, digitalis, or beta-blockers) at least 48 hours before the procedure. Only chronic amiodarone was allowed. The subsequent 41 patients (Group B), in addition to previous prescriptions, were advised to take an intracellular calcium-lowering drug (verapamil, 120 mg twice daily for 3 days before low energy intracardiac cardioversion); after restoring sinus rhythm the drug was maintained for another 7 days. Sixteen patients in Group A and 14 in Group B were on chronic treatment with amiodarone. All these patients continued amiodarone (200 mg daily) after low energy intracardiac cardioversion. All the other Group A and Group B patients, not on amiodarone, were treated, after low energy intracardiac cardioversion, with propafenone (from 450 to 900 mg daily according to body weight).

Table I. Underlying heart disease.

Heart disease	Group A (n=41)	Group B (n=41)
Systemic hypertension	21	21
Ischemic heart disease	3	2
Dilated cardiomyopathy	3	3
Mitral valve disease	6	4
No cardiac pathology	8	11

Each patient was placed on anticoagulant therapy using acenocoumarol at the doses necessary in order to maintain INR values between 2 and 3 for at least 1 month before low energy intracardiac cardioversion.

Anticoagulant therapy was suspended the day before the procedure only if the INR was above 2.5. However, at the time of the procedure, no patient was rejected because of abnormal INR values. Anticoagulant therapy was usually resumed the evening after the procedure and maintained (in the therapeutic range) for at least 1 month.

The low energy intracardiac cardioversion procedure consisted of a few sequential actions. Local anesthesia using 2% lidocaine was administered at the right inguinal area. A standard tetra or bipolar catheter was inserted via the right femoral vein into the apex of the right ventricle in order to synchronize the electric shock with ventricular depolarization and for backup pacing. At the same site, two 8F large surface area electrodes (Transvene 6933-110 or indifferently Transvene 6937-110, Medtronic Inc., Minneapolis, MN, USA) were also inserted to perform cardioversion. The two leads were positioned at two different sites: the first one in the upper right atrium with the tip located within the appendage and the shaft along the lateral wall; the second one was positioned, without predetermined choice, either into the coronary sinus (RA-CS), or the left branch of the pulmonary artery (RA-LPA). The same venous access was usually used for the right ventricular lead and the right atrial defibrillation lead. In order to facilitate the manipulation of the catheters, a second venous access site, through the same femoral vein, was used for the second defibrillation catheter.

Energy was delivered from a defibrillator support device (Medtronic model DISD 5358) that allowed selection of designated energy levels and displayed the impedance of the circuit and the amount of energy actually delivered at each discharge. Biphasic, truncated 65% tilt asymmetric pulses were delivered. After an initial shock at 0.2 J, necessary in order to test for impedance, shocks were delivered in sequence at increasing programmed energy levels of 8, 10, 13, 15 and 20 J. The procedure

was stopped as soon as the sinus rhythm or the maximal programmed energy level was reached.

At the beginning of the procedure, the patient was mildly sedated using diazepam. Sedation could be repeated during the procedure itself, depending on the patient's anxiety and acceptance of discomfort. Five minutes prior to the first shock, propafenone (1.5 mg/kg i.v.) was administered to each patient. As soon as sinus rhythm was restored, an intravenous infusion containing a fixed dose of 70 mg of propafenone was started and completed in 1 hour. We resorted to propafenone treatment in a further attempt to prevent the early recurrence of AF. The patient's ECG was monitored until he was discharged, usually 4-6 hours following removal of the catheters. At that time, a final 12-lead ECG was obtained. In order to verify the persistence of sinus rhythm, the patient was submitted to conventional 12-lead ECG on the first, seventh and thirtieth days following the procedure.

Statistical analysis. Continuous variables were compared using the unpaired Student's t-test and values are expressed as mean ± SD or as percentages.

Results

Cardioversion successfully restored sinus rhythm in 80 patients (97.6%). In 1 patient, for successful restoration of sinus rhythm it was necessary to modify the electrode configuration from RA-LPA to RA-CS.

The mean number of shocks attempted for each patient was 2.3 (range 1- 5). In 34 patients (41.5%) sinus rhythm was restored at the first attempt with the energy level set at 8 J. In 2 patients (2.4%) all attempts to restore sinus rhythm were ineffective.

The mean delivered energy was 10.5 J (range 7.2-19.8 J). The mean impedance at the maximum energy delivered was 50.0 Ohms (range 26-80 Ohms). Comparison of the RA-CS and RA-LPA configurations revealed that, except for impedance which was higher in the RA-LPA configuration ($p < 0.001$), no other parameter reached a statistically significant difference (Table II).

No statistically significant differences were found between Group A and Group B in comparing the energy levels and the number of attempts (Table III).

In 7 cases, it was necessary to replace one or both defibrillation catheters due to dislocation of the leads: the protocol was then restarted where it was interrupted.

The mean dose of diazepam used during the procedure was 12.1 mg (range 5-25 mg). The mean fluoroscopy time necessary to complete the procedure was 6.3 min (range 2-17 min).

Evaluation of the patients' clinical follow-up data yielded the following results: in Group A, 23 patients (56.1%) had recurrence of AF at 1 month in spite of adequate pharmacological treatment with amiodarone (8 patients) or propafenone (15 patients). One of the patients presented with immediate AF recurrence and another patient, 3 hours after low energy intracardiac cardioversion; 2 patients showed AF the day following low energy intracardiac cardioversion; in 14 patients, AF recurrence was diagnosed 7 days after the procedure and, in the remaining 5, recurrence of this arrhythmia was diagnosed at 1 month of follow-up. Thus, in 18 patients (78.3% of all the patients who presented with relapse of AF within the end of follow-up) AF recurrence was diagnosed

Table II. Comparative results between the right atrium-coronary sinus (RA-CS) and the right atrium-left pulmonary artery (RA-LPA) electrode configurations.

Electrode configuration	Shock energy (J)	Shock impedance (Ohms)	No. shocks
RA-CS (n = 46)	10.0 ± 3.3	47.7 ± 8.8	2.2 ± 1.3
RA-LPA (n = 35)	10.9 ± 4.3	55.5 ± 9.2	2.4 ± 1.5
p	NS	< 0.001	NS

Table III. Comparative results between Group A and Group B in the right atrium-coronary sinus (RA-CS) and the right atrium-left pulmonary artery (RA-LPA) electrode configurations.

	RA-CS		RA-LPA	
	Shock energy (J)	No. shocks	Shock energy (J)	No. shocks
Group A (n = 41)	10.2 ± 3.0	2.3 ± 1.3	10.6 ± 3.9	2.3 ± 1.4
Group B (n = 41)	9.9 ± 3.5	2.0 ± 1.4	11.3 ± 4.9	2.5 ± 1.7
p	NS	NS	NS	NS

within 7 days of the procedure. In Group B, 21 patients (51.2%) had AF recurrence within 1 month of the procedure. Nine of these patients were on amiodarone and 12 on propafenone. Among these, 2 showed early recurrence, 4 patients presented with AF the day after the procedure, 10 patients after 7 days and the last 5 patients at 1 month of follow-up. In 2 patients all attempts to recover sinus rhythm were ineffective. Thus, in 16 patients of Group B (76.2% of all the patients who presented with AF relapse within the end of follow-up) AF recurrence was diagnosed within 7 days of the procedure when, in accordance with the protocol, verapamil treatment was stopped. Five patients in Group A and 5 in Group B (respectively 21.7 and 23.8% of all the patients in each group who presented with AF relapse) had AF recurrence between 7 days and 1 month after low energy intracardiac cardioversion.

No difference between the two groups was statistically significant.

In these series no adverse events related to the antiarrhythmic treatment were observed. Bradycardia, which however did not necessitate any modification in the drug treatment regimen, was occasionally observed in Group B patients.

Discussion

In recent years AF has aroused renewed interest due to its significant clinical, socio-economic and therapeutic impact.

New pharmacological (ibutilide, dofetilide, etc.) and non-pharmacological (radiofrequency catheter ablation, pacing with different algorithms or multisite, atrial defibrillator, etc.) strategies and therapeutic options to prevent AF or achieve cardioversion are currently rapidly expanding.

The restoration and maintenance of sinus rhythm are the first endpoints in the treatment of this arrhythmia.

The aim of our study was to evaluate in a prospective, non-randomized fashion whether the efficacy of the treatment with conventional class IC or III antiarrhythmic drugs in reducing AF recurrences after low energy intracardiac cardioversion can be improved by the addition of verapamil.

In our study group, patients with chronic AF (lasting > 1 month) were included. Acute resolution of arrhythmia was achieved in 97.6% of cases. In more than 40% of the patients successful cardioversion was achieved by delivering just one shock.

Despite the good acute results of low energy intracardiac cardioversion, the persistence of a normal sinus rhythm after the procedure was not satisfactory. This fact could be attributed to the mechanism of induced electrical remodeling. The electrical remodeling of the atria results in a reduction of the atrial refractory periods, loss of the physiologic rate-dependent adaptation of the refractory periods and consequently in a shortening of the wavelength of the atrial impulses. This can explain the increased vulnerability to recurrence of AF after cardioversion, even though the mechanism of electrical remodeling is incompletely understood[21-23]. The recovery from the electrical remodeling seems to be completely reversible within 1 week of restoration of sinus rhythm[19,20]. For this reason the incidence of the AF recurrence diminishes after the first 7 days. Some authors[24-27] reported, in animal and human studies, that when administered during AF, drugs which decrease the intracellular calcium concentration also reduce electrical remodeling. Following cardioversion, this would lead to a more rapid recovery of atrial cells from electrical remodeling. Therefore, they suggest the use of intracellular calcium-lowering drugs in this setting.

However, the beneficial role of verapamil in the prevention of atrial electrical remodeling, in particular in patients with chronic AF, is still unclear and controversial.

In a recent review, Lee et al.[29] evaluated the most relevant studies regarding the tachycardia-induced changes in the atrial electrophysiological properties and particularly atrial remodeling. In animal models and in human studies it has been demonstrated that following short-lasting AF or rapid atrial pacing, the effective atrial refractory period shortens significantly with full recovery within a few minutes. On the contrary, after long-lasting AF or prolonged atrial pacing, reversal of the shortening of the effective atrial refractory period might necessitate months. Data in various animal and human studies regarding the changes in the dispersion of the atrial effective atrial refractory period and in the intra-atrial conduction velocity are also controversial.

These divergent results might be due to the different protocols used. Furthermore, a site-dependent difference in atrial electrical remodeling was demonstrated in humans[30]. However, studies about the dispersion of the effective atrial refractory period in patients with chronic AF have not been consistent. The effects of calcium channel blockers on the conduction velocity or the effective refractory period of atrial cells in chronic AF are still inconclusive. This calls for further prospective studies.

Our prospective study was performed on two subsequent groups of patients similar for age, pathology, duration of AF and therapeutic strategy (propafenone or amiodarone) employed for the prevention of AF recurrences after low energy intracardiac cardioversion. The only difference between the two groups consisted of the fact that oral verapamil, starting 3 days before low energy intracardiac cardioversion and continued for 1 week after the procedure, was administered only to Group B patients.

Our study did not show a statistically significant difference between Group A and Group B regarding the recurrence of AF. To our knowledge, it is not clear whether the association between verapamil and other antiarrhythmic drugs might modify the expected prophylactic activity of verapamil alone.

The decision to start verapamil therapy only 3 days before low energy intracardiac cardioversion and to stop the drug 1 week after the procedure might have interfered with the results of our study. A very similar strategy was, however, adopted by De Simone et al.[28]. During a follow-up period lasting 3 months, these authors diagnosed AF recurrence in 23.7% of the patients; 62.2% of the AF relapses occurred during the first week. The incidence of AF recurrence was significantly higher in patients treated with propafenone only compared with patients treated with oral verapamil alone or verapamil combined with propafenone.

In our study, short-term recurrence of AF (at 1 month) was observed, not only in more than 50% of patients under prophylactic treatment using either propafenone or amiodarone (Group A), but also in patients in whom verapamil was associated with the abovementioned drugs (Group B). Such a high percentage of recurrences, in agreement with other authors' reports[19,31,32], was probably due to the fact that our series included only patients with long-standing AF. This could also explain the disagreement of our data with the results of other studies such as the retrospective study by Tieleman et al.[24,25] and the prospective study by De Simone et al.[28]. These latter articles documented that the use of verapamil during AF, alone or associated with other antiarrhythmic drugs, can reduce the incidence of early AF recurrences.

Our data could be in agreement with the results of a recent experimental study by Lee et al.[32] that showed that in dogs, verapamil not only cannot prevent the long-term tachycardia-induced changes in atrial electrophysiological properties, but also increases the duration of AF.

More recently, Pandozi et al.[33] showed that in humans, the long-term administration of verapamil before internal cardioversion not only does not prevent electrical remodeling, but also increases the likelihood of the early recurrence of AF by shortening the effective refractory period of atrial cells. These results, which are in contrast with those of previous studies, could be explained by the different time of onset of AF. Verapamil could be useful before or shortly after the onset of arrhythmia but would be completely ineffective in case of long-lasting AF when electrical and structural remodeling are already present. Indeed, verapamil does not affect the inequality in the recovery of excitability in the right atrium. In conclusion, these authors suggest that, in patients with persistent AF, verapamil should favor rather than prevent the recurrence of AF after cardioversion.

On the other hand, verapamil can exert favorable effects by inducing the reversal of the structural modifications of atrial cells which can lead to the atrial myopathy.

Our results do not suggest that verapamil favors the recurrence of AF after low energy intracardiac cardioversion when the drug is administrated for a short time. In Group B patients, the addition of verapamil to propafenone or amiodarone was not associated with adverse events. Bradycardia, which however did not necessitate any modification in the drug treatment regimen, was occasionally observed.

The quantity of energy, the RA-CS or RA-LPA configurations and the number of attempts necessary in order to achieve cardioversion did not show statistically significant differences between Group A and Group B patients and do not seem to interfere with the number of AF recurrences.

This study has several potential limitations:

- the interpretation of the results can be difficult because a randomized placebo-controlled group is lacking and because the antiarrhythmic therapy before cardioversion was not homogeneous;
- data regarding the left atrial size could be useful for a better understanding of our results, but are not available;
- data on the refractory periods and conduction velocity are also unavailable;
- the number of patients in the two groups is relatively low.

Despite these limitations, the results of our study suggest that short-term treatment with verapamil is useless for the prevention of AF recurrence after low energy intracardiac cardioversion. Further larger studies will be useful to show the effect of verapamil in the prophylaxis of AF recurrences after cardioversion.

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