Postcardioversion Atrial Electrophysiologic Changes Induced by Oral Verapamil in Patients With Persistent Atrial Fibrillation

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OBJECTIVES
The aim of our study was to verify the effect of oral administration of verapamil on atrial electrophysiologic characteristics after cardioversion of persistent atrial fibrillation (AF) in humans.

BACKGROUND
Discordant findings have been reported regarding the efficacy of verapamil in preventing the electrical remodeling induced by AF.

METHODS
We determined the effective refractory periods (ERPs) at five pacing cycle lengths (300 to 700 ms) and in five right atrial sites after internal cardioversion of persistent AF (mean duration 238.1 ± 305.9 days) in 19 patients. Nine patients received oral verapamil (240 mg/day) starting four weeks before the electrophysiologic study, whereas the other 10 patients were in pharmacologic washout.

RESULTS
The mean ERPs were 202.0 ± 22.7 ms in the washout group and 189.3 ± 18.5 ms in the verapamil group (p < 0.0001). The degree of adaptation of refractoriness to rate was similar in the two groups (mean slope value in the washout group and verapamil group: 0.07 ± 0.03 and 0.08 ± 0.05, respectively), showing a normal or nearly normal adaptation to rate in the majority of the paced sites in both groups. The mean ERP was slightly longer in the septum than in the lateral wall and in the roof, both in the washout and verapamil groups.

CONCLUSIONS
In patients with persistent AF, long-term administration of verapamil before internal cardioversion resulted in 1) shortening of atrial ERPs; 2) no change in refractoriness dispersion within the right atrium; and 3) no change in atrial ERP adaptation to rate.

Several studies, both in animals and humans, have demonstrated that high atrial rates, such as those determined either by spontaneous and induced atrial fibrillation (AF) or by rapid atrial pacing, lead to a shortening of the atrial effective refractory period (ERP) (1–4). This condition could facilitate the maintenance of the arrhythmia and its recurrence after sinus rhythm restoration. Subsequent experimental and human studies have shown that this phenomenon, called “electrical remodeling,” could be prevented by the administration of verapamil (5–9). However, in two recent reports (10,11), verapamil administered after the initiation of AF actually caused a shortening of the local fibrillation cycle length (a variable that is closely correlated with the atrial ERP) in both the animal model and in patients with persistent AF. This new finding is confounding and suggests that the drug might reduce, rather than increase, the chances of spontaneous termination of the arrhythmia and facilitate, rather than prevent, its recurrence after cardioversion.

However, the aforementioned studies are very dissimilar in terms of the type of the arrhythmia (high rate of atrial pacing, spontaneous or induced AF of variable duration), the species studied (humans, dogs and goats) and the timing of drug administration (before or after the arrhythmia onset). These differences could account for the discordant effects of verapamil on atrial electrophysiologic characteristics. Moreover, even the results of clinical studies on the effect of verapamil on AF termination and recurrence are confounding. Some of them have shown no beneficial effect of verapamil (12,13), whereas others (14,15) have demonstrated a drug-induced reduction of the early recurrences of the arrhythmia. This beneficial effect has been attributed to a verapamil-mediated attenuation of the atrial electrical remodeling. Therefore, because of the incomplete and discordant reports on this subject, and in order to be close to the clinical ground, the present study was designed to evaluate the effects of oral administration of verapamil on the atrial electrophysiologic characteristics in patients with persistent AF. Thus, the following variables were evaluated immediately after electrical cardioversion: atrial refractoriness, atrial refractoriness dispersion and atrial refractoriness response to abrupt cycle length changes.

METHODS

Patient selection. The study included 30 consecutive patients with persistent AF (duration between 30 days and 3 years), referred to our Institute for cardioversion of the arrhythmia. To be included in the study, the patients must not have had a previous cardioversion attempt, either
pharmacologic or electrical; they had to be off antiarrhythmic drugs; and they had to be in New York Heart Association functional class I or II, with no clinical or instrumental signs of cardiac insufficiency. The eligible patients were scheduled for a study protocol that included internal electrical cardioversion followed by an electrophysiologic study. Two patients with a contraindication to the use of verapamil and two patients who refused to accept the protocol were excluded from the study. The remaining 26 patients were randomly assigned to receive either no antiarrhythmic drugs (e.g., calcium antagonist, digoxin, beta-blockers) or verapamil (240 mg/day) for three weeks before endocavitary cardioversion. During this period, they were also fully anticoagulated. The study was approved by our Institutional Ethical Committee, and all the patients gave their written, informed consent.

The diagnosis of AF was based on the surface electrocardiogram with the following criteria: presence of fluctuation from baseline without regular P or F waves and totally irregular RR intervals. These criteria had to be validated by endocardial recordings showing variability of the beat-to-beat cycle length, morphology and/or the amplitude of recorded bipolar atrial electrograms (16).

Thyroid dysfunction had been ruled out in all patients. As a rule, after completion of the protocol, all the patients were treated with intravenous propafenone (2 mg/kg body weight), followed by oral administration of the drug (600 to 750 mg/day).

**Electrophysiologic study.** Two catheters were used for each patient; they were introduced in the same sheaths used for the leads necessary for internal cardioversion. A standard quadripolar lead with 2-mm spacing (Bard-USCI Inc., Lowell, Massachusetts) was positioned in the right atrium, allowing contemporary recording of bipolar electrograms from the distal and proximal pairs. In the right atrium, a Franz catheter (EP Technologies, San Jose, California) was also positioned. This was preferred because of its low pacing threshold. The study was performed 5 min after low energy internal cardioversion.

In each patient, up to five right atrial sites, depending on the time needed for the procedure, were mapped in the 30° left anterior oblique view. The mapped sites were the following: mid lateral wall, low lateral wall, high lateral wall, atrial roof and septum.

**Follow-up.** After the study, all the patients were treated long term with propafenone (450 mg/day in three divided doses). Moreover, the patients in the verapamil group continued the drug at the same dosage. All the patients visited the Outpatients Clinic one week, one month and six months after the study.

**Stimulation protocol.** The stimulation protocol has been previously described in detail (17). Briefly, the Franz catheter was used for pacing by delivering a square wave of 2-ms pulse duration at twice the stimulation threshold. At each site, the ERP was measured at basic cycle lengths of 300, 400, 500 and 600 ms, and, when possible, in relation to the sinus rate, at 700 ms, by the decremental extrastimulus method using steps as short as 2 ms. The ERP was then calculated after a short–long (eight basic drive beats at 300 ms followed by a 600-ms premature beat) and a long–short (eight basic drive beats at 600 ms followed by a 300-ms premature beat) sequence and compared with the ERP at basic cycle lengths of 600 and 300 ms, respectively. The stimulation protocol was performed in random order either clockwise (from the low lateral atrial wall to the septum) or counterclockwise (from the septum to the low lateral atrial wall). According to our protocol, the study was stopped if pacing or programmed stimulation re-induced AF or other sustained atrial arrhythmias, requiring cardioversion. Patients were considered for data analysis only when the protocol was completed at least in two sites; otherwise, the patient was considered a dropout.

**Statistical analysis.** All data, unless otherwise noted, were expressed as the mean value ± SD. For intrapatient effects of washout or verapamil, analysis of variance (ANOVA) with repeated measures was used to compare mean values of atrial ERP between the different basic cycle lengths of pacing and after the short–long and the long–short sequence. When significant differences were detected, the data were analyzed by paired the Student t test, and the probability value was corrected by multiplying it for the number of comparisons (Bonferroni correction). The differences of the measured numeric data between the washout and verapamil groups were analyzed by the unpaired t test. The mean values of ERP in different atrial sites within the same group of treatment (e.g., verapamil or washout) were analyzed by the unpaired Student t test, and the probability value was corrected by Bonferroni correction. The dispersion of atrial refactoriness (the longest ERP minus the shortest ERP) was determined at the different basic cycle lengths.

Differences in categoric variables were analyzed by the chi-square test with Yates’ correction or the Fisher exact test. The relation between the mean ERP in each patient and the duration of AF was studied by single linear regression analysis. The results were considered to be statistically significant at p < 0.05.

For each paced site, the linear correlation between the ERPs and the corresponding pacing rates was calculated by single linear regression analysis. The presence of normal or abnormal refactoriness adaptation to rate and its degree were also established by evaluating the slope values. According to the slope figures, the adaptation of the ERP to rate was considered absent when the slope value was zero, and inverted if its value was negative. For positive values between 0.01 and 0.04, the adaptation was considered poor; for values between 0.05 and 0.06, it was considered nearly
normal; and for values \( \geq 0.07 \), it was classified as normal (17,18). The analysis was performed using the statistical software GB-STAT (version 6.5.4).

RESULTS

Patients and paced sites. Three of the 26 patients selected for the study (one in the washout group and two in the verapamil group) were found to be in sinus rhythm at the time of the scheduled cardioversion. In two of the remaining 23 patients (one in the washout group and one in the verapamil group), internal cardioversion was followed by immediate recurrence of AF. Therefore, 11 patients in the washout group and 10 patients in the verapamil group were studied. The study groups were comparable in terms of baseline clinical characteristics (Table 1).

In two of the 21 patients, the study was stopped because of the induction of sustained AF during the first or the second stimulation sequence in the first paced site. One of these patients was in washout and one was taking verapamil. Thus, the stimulation protocol was carried out in 19 patients: 10 in washout and 9 taking verapamil. It was performed in all five sites in 15 patients (eight in washout and seven taking verapamil); in four sites in two patients (one in washout and one taking verapamil); in three sites in one patient in washout; and in two sites in one patient taking verapamil—for a total of 88 sites. In two patients (one in washout and one taking verapamil), the sequence at the 700-ms cycle length was not performed because of the higher sinus rate.

Table 2 reports the sites where the stimulation was performed in both the washout and verapamil groups.

Refractoriness and adaptation of ERPs to rate. The mean ERPs at the different stimulation cycle lengths, taking into account all of the paced sites in both the washout and verapamil groups, are reported in Table 3. The mean ERP of the total group was significantly shorter in the verapamil group than in the washout group (189.1 ± 17.3 vs. 202.0 ± 22.7 ms, \( p < 0.0001 \); this finding was present in all of the stimulation cycles.

No relation was found between the duration of the AF episode and the mean ERP, as studied in each patient (\( r = 0.049, p = 0.8 \)).

As graphically shown in Figure 1, there was a linear correlation between the mean atrial ERPs and the stimulation rate in both groups (\( r = 0.90 \) in the washout group and \( r = 0.94 \) in the verapamil group). The mean slope value was 0.07 ± 0.03 in the washout group and 0.08 ± 0.05 in the verapamil group.

Considering the individual stimulation sites, slope values \( \geq 0.07 \) were present in 24 sites (51%) in the washout group and 18 sites (44%) in the verapamil group; slope values between 0.05 and 0.06 were found in 12 sites (26%) in the washout group and 12 sites (29%) in the verapamil group; slope values between 0.01 and 0.04 were found in 11 sites (23%) in the washout group and 10 sites (24%) in the verapamil group; and a slope value of 0 was found in one site (3%) of one patient in the verapamil group. No negative slope values were found in any site. Therefore, a normal or nearly normal adaptation to the rate was present in 67 sites (76%): 36 sites (77%) in the washout group and 31 sites (75%) in the verapamil group (\( p = 0.8 \)).

Refractoriness dispersion. As shown in Table 4, the mean ERPs were shorter in the lateral right atrial sites and in the roof than in the septum, both in the washout and in the verapamil groups; these differences reached statistical significance when the septum was compared with the mid lateral wall and the roof.

The spatial dispersion of refractoriness at the various basic cycle lengths was similar between the two groups.

Effect of abrupt cycle length changes. The effects of the long–short and short–long sequences on ERPs are shown in Table 5.

In the washout group, the mean ERP after the long–short sequence (basic cycle length of 600 ms followed by a beat at 300 ms) was significantly shorter than the ERP during constant pacing at 300 ms (166.3 ± 10.4 ms vs. 185.7 ± 18.0 ms, \( p < 0.0001 \)) (Fig. 2), implying an overshoot of the adaptation of refractoriness to the preceding premature beat. The overshoot was not bidirectional; in fact, no difference was found between the atrial ERP during the short–long sequence (basic cycle length of 300 ms followed by a beat at 600 ms) and the ERP during constant pacing at 600 ms (201.3 ± 18.7 ms vs. 209.4 ± 21.4 ms, \( p = 0.1 \) ) (Fig. 2). In the verapamil group, the mean ERP after the long–short sequence was also significantly different from the
ERP during constant pacing at 300 ms (168.5 ± 12.3 ms vs. 175.2 ± 13.2 ms, p < 0.03) (Fig. 3). However, the degree of the overshoot was greater in the washout group than in the verapamil group (mean ERP variation: 9.8% vs. 3.4%, p < 0.0001). The mean ERP during the short–long sequence and the ERP during constant pacing at 600 ms were not significantly different in the verapamil group (203.4 ± 19.4 ms vs. 197.6 ± 17.3 ms, p = 0.2) (Fig. 3).

**Follow-up.** At one-month follow-up, AF recurrences were observed in six patients (60%) in the washout group and in two patients (20.2%) in the verapamil group (p = 0.2), whereas at six months, the recurrence rate was 70% (7 of 10 patients) in the washout group and 40.4% (4 of 9 patients) in the verapamil group (p = 0.5).

**DISCUSSION**

**Main findings.** In this study, we have demonstrated that verapamil, when administered after AF onset, not only does not prevent atrial electrical remodeling, but actually causes a shortening of atrial ERPs. This behavior is opposite of that described in the published data, both in animals and humans, when the drug is given before the beginning of either induced AF or high rate pacing. Moreover, long-term verapamil administration has no effect on adaptation of refractoriness to rate in this specific subset of patients, and it does not seem to have any effect on refractoriness dispersion. Furthermore, the abnormal overshoot in refractoriness adaptation after a long–short sequence that is present in patients in washout became reduced in patients treated with the drug.

**Effects of high rates on transmembrane ionic currents.** Previous experimental studies have demonstrated that rapid and irregular depolarizations can increase cytosolic Ca\(^{2+}\) in cardiac myocytes of many different species (19,20). In turn, intracellular Ca\(^{2+}\) overload was shown to reduce both the L-type Ca\(^{2+}\) current (ICa) (21,22) and the transient outward K\(^+\) current (Ito) both in atrial and ventricular myocytes (23–25). Moreover, in atrial appendages of patients with chronic AF, there was a downregulation of the expression of the alpha-subunit of the Kv 1.5 protein, which is responsible for the ultrarapid component of the delayed rectifier current (IKur), leading to a reduction of the outward K\(^+\) current densities (26). Indeed, it is worth noting that after rapid and/or irregular depolarizations, the degree of reduction in the specific current flows differs in the two cardiac chambers (27,28). In the atria, a reduction in ICa is prevalent, accounting for the shortening of action potential and refractoriness duration, whereas in the ventricle, the reduction in Ito is more important, leading to a prolongation of the aforementioned variables.

**Effect of verapamil on atrial ERPs.** Several studies have been performed to evaluate whether the L-type calcium
channel blocker verapamil could counteract atrial refractoriness changes induced by high atrial rates. Tielemans et al. (5) showed in goats that electrical remodeling of the atrium induced by rapid atrial pacing was significantly attenuated by verapamil infusion started 4 h before the stimulation. Goette et al. (6) reported that in dogs subjected to 7 h of atrial pacing at 800 beats/min, atrial electrical remodeling was blocked by verapamil administered as an intravenous bolus (followed by continuous infusion) 30 min before the high frequency pacing. Daoud et al. (7) and Yu et al. (8) reported that in humans, ERP shortening, after brief episodes of pacing-induced AF, was markedly attenuated by verapamil infusion given before the induction of the arrhythmia. On the basis of these results, it was suggested that the drug could be clinically effective in preventing immediate recurrence of AF after cardioversion or in reducing the duration of AF paroxysms (5–8).

Our findings were substantially different: verapamil, when administered after the onset of persistent AF, actually shortened the postcardioversion atrial ERPs, thus possibly reducing the chances of spontaneous termination of the arrhythmia and increasing the likelihood of its early recurrence after cardioversion.

These opposite findings could be explained by the different timing of the drug administration in relation to the onset of the arrhythmia. It could be that verapamil may prevent the electrical remodeling when given before or shortly after the onset of high atrial rates (rapid pacing or AF), but it is totally ineffective or even has a paradoxical worsening effect when given after high atrial rates have already been established and electrical (and possibly structural) remodeling is already present. In support of this hypothesis, Ramanna et al. (10) observed that in patients with chronic AF, early infusion of verapamil determined a shortening of the mean fibrillatory interval, an index of the local refractory period, whereas Duytschaever et al. (11), in a goat model of paroxysmal AF, observed that verapamil infusion shortened the AF cycle length and changed paroxysmal into chronic AF when given intravenously after 24 h of electrically maintained AF. Recently, Sato et al. (29), when administering oral verapamil to patients with chronic AF, found no difference in their atrial refractory periods after cardioversion, as compared with patients in washout. The recovery from electrical remodeling was indeed delayed in patients taking verapamil. On the basis of these results, it is conceivable that verapamil could have different biochemical effects on high rate–activated atrial cells in relation to the timing of its administration. When administered before high rate cell stimulation, the drug could prevent calcium overload and the consequent reduction of ICa. This effect probably outweighs the ICa reduction because of the direct effect of the drug on sarcoplasmic L-type calcium channels (30), and thus prevents ERP shortening. In contrast, when electrical remodeling has already occurred, verapamil could not totally reverse the calcium overload, and the prevalent effect of the drug could be a further reduction of ICa, owing to the direct action of verapamil on the L-type calcium channels. This leads to a further shortening of the plateau phase of the monophasic action potential duration and, hence, of refractoriness. Moreover, it is known that although short-lasting high rate depolarization shortens ERPs by direct Ca2+-induced ICa inhibition (31), in patients with long-lasting AF, a further contribution to persistent ERP shortening is also caused by a decrease in messenger ribonucleic acid levels of the L-type calcium

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**Table 4.** Atrial Effective Refractory Periods in Different Right Atrial Sites in Washout and Verapamil Groups

<table>
<thead>
<tr>
<th>Paced Sites</th>
<th>Stimulation (p Value)</th>
<th>Cycle Length (600 ms)</th>
<th>Length (p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washout</td>
<td>185.7 ± 18.0</td>
<td>166.3 ± 10.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Verapamil</td>
<td>175.2 ± 13.2</td>
<td>168.5 ± 12.3</td>
<td>0.03</td>
</tr>
<tr>
<td>All</td>
<td>180.8 ± 16.7</td>
<td>167.6 ± 11.5</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD, unless otherwise indicated.
channels, leading to downregulation of the channels’ density (32). In this case, a more marked effect on repolarization could be expected, because there is a direct drug-mediated effect of \( I_{Ca} \) on a reduced number of \( \text{L-type} \) channels.

However, keep in mind that the difference in refractoriness between the washout and verapamil groups could be explained, at least in part, by increased refractoriness in the washout group, related to impaired left ventricular function due to higher ventricular rates, as reported by Li et al. (33) in the setting of heart failure at high rates in dogs. Nevertheless, none of our patients had clinical signs of heart failure, and recently left ventricular dysfunction was found to have no effect on atrial refractoriness in dogs (34).

**Effect of verapamil on ERP adaptation to rate.** According to the slope values, a normal or nearly normal adaptation to the stimulation rate was found in the majority of atrial sites, both in the washout and verapamil groups. In fact, no significant difference was found in the mean slope value between the two groups. This results are in agreement with previous reports of our group, which have shown, after cardioversion of persistent AF, a normal or nearly normal refractoriness adaptation to the stimulation cycle, both in patients in washout and in patients pretreated with ami-darone (17). The fact that the patients pretreated with verapamil have a similar behavior confirms these results and suggests that verapamil has no effect on the ERP adaptation to rate, contrary to what has been previously reported in animals (5). In fact, the number of sites with normal, nearly normal, poor and no adaptation to rate was similar in the washout and verapamil groups.

**Effects of verapamil on refractoriness dispersion.** In our study, the ERPs were found to be shorter in the lateral right atrial wall and in the roof than in the septum, both in the washout and verapamil groups. Moreover, the degree of refractoriness dispersion was not significantly different between the two groups, implying that pretreatment with verapamil does not affect the inhomogeneity of recovery of excitability within the right atrium.

Our results are somehow different from those of a recent report showing that verapamil infusion in patients with chronic AF increased refractoriness dispersion between the lateral wall and the right atrial appendage (10). In this study, refractoriness dispersion was evaluated by calculating the coefficient of dispersion (standard deviation of all mean fibrillatory intervals expressed as a percentage of the overall mean fibrillatory interval). The differences in the mode of drug administration in the right atrial sites studied and in the methods for determination of refractoriness dispersion could account for the different results.

**Effect of abrupt cycle length changes on refractoriness.** It is known that the ERP of normal atrial myocardium abruptly and appropriately adjusts to the duration of the last cycle (35,36). We have previously demonstrated (17) that after cardioversion of persistent AF, atrial refractoriness shows an abnormal overshoot in adaptation after a long–short sequence. This phenomenon may have clinical relevance because it could contribute to the frequent recurrence of the arrhythmia in the first days after cardioversion and has been confirmed in the patients in washout in the present study. Moreover, an abnormal overshoot in atrial refractoriness adaptation after a long–short sequence was found also in patients pretreated with verapamil before cardioversion. However, the degree of the overshoot was less prominent, implying a possible favorable action of the drug on this abnormal behavior.

**Follow-up.** The patients treated with both propafenone and verapamil had less recurrence of AF as compared with those patients treated with propafenone alone, but the numbers are too small to permit any significant conclusion. The study, however, was not designed as a follow-up study.

**Clinical implications.** The results of clinical studies on the effect of verapamil on AF termination and on its recurrence rate are not uniform in the published data. A recent study (14) concluded that treatment with drugs that reduce Ca\(^{2+}\) entry decreases the recurrence rate of the arrhythmia. Actually, it was a nonrandomized, retrospective study, and patients in the control group were taking digoxin in the majority of cases; therefore, it is not possible to determine whether the lower recurrence rate observed in the treated group was the consequence of the administration of calcium antagonist drugs or the effect of a possible digoxin proarrhythmic action in the other group. More recently, De Simone et al. (37) demonstrated that the addition of verapamil to propafenone three days before cardioversion in patients with persistent AF reduced the incidence of early recurrence of AF, as compared with propafenone alone. In contrast, other studies have shown no effect (13) or a worsening action of verapamil on AF duration and recurrences (12).

The main result of our study—further shortening of atrial ERPs—suggests that verapamil should favor rather than
prevent the recurrence of the arrhythmia after cardioversion in patients with persistent AF. However, it has to be considered that verapamil could theoretically exert even favorable effects in patients with AF: it could determine the reversal of the structural and ultrastructural cellular changes (6,38,39) and of the atrial morphologic modifications (40) related to the development of an atrial tachymyopathy. Recently, Haissaguerre et al. (41) have shown that radiofrequency ablation of triggering atrial ectopic beats originating from foci located in the pulmonary veins eliminated AF recurrences in 62% of the patients. Verapamil could suppress the firing of the atrial foci, triggering AF recurrences, thanks to its action on abnormal automaticity and on early and delayed afterdepolarization (42). Moreover, our finding that the drug reduces the degree of the overshoot after a long–short sequence could have some protective role. Therefore, future randomized, prospective studies are needed to establish the actual effect of verapamil on AF recurrences and the electrophysiologic mechanisms accounting for this effect.

Study limitations. First, our results are limited to the right atrium, because no left atrial site was considered in the study. Second, the protocol was discontinued in patients with re-induced AF, so that patients with the higher atrial vulnerability were excluded. Nevertheless, the protocol was completed in at least two sites in 90% of the studied patients, and therefore our observation is applicable to the majority of patients with persistent AF. Third, conditioning pacing trains, which have been demonstrated to be useful in improving the reproducibility of ventricular ERPs, were not used in this study because of the long duration of the stimulation protocol.

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