Daily oral verapamil before but not after rapid atrial excitation prevents electrical remodeling

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Received 3 September 2001; accepted 16 January 2002

Abstract

Background: Intravenous verapamil has been reported to prevent electrical remodeling induced by rapid atrial excitation of several minutes to several hours. However, the clinical efficacy of verapamil when taken orally and daily remains controversial. Purpose: We attempted to demonstrate our hypothesis that if verapamil prevents calcium (Ca) overload, its efficacy would be greater when taken before, rather than after, the onset of rapid atrial excitation. Methods: In 24 dogs, pacing and recording electrodes were sutured onto the right atrium. After a 5-day recovery period, rapid atrial pacing at 400 ppm was started, followed 2 days later by oral verapamil (8 mg/kg per day) in eight dogs (After group; A). In another eight dogs, oral verapamil administration was begun 1 week before the initiation of rapid pacing (Before group; B). In the remaining eight dogs, only rapid atrial pacing was started, without oral verapamil (Control group; C). We measured the effective refractory period (ERP) and conduction velocity (CV), and calculated wavelength (WL) at cycle lengths 200 and 300 ms on the day before (P0), and after 2 (P2), 7 (P7), 14 (P14) days of rapid pacing. Results: In response to rapid atrial pacing, ERP, CV, WL decreased and progressively and comparably in A and C (P < 0.05 vs. P0). In contrast, in B, these parameters did not change significantly and remained greater than those in A and C (P < 0.05). Moreover, the adaptation of ERP to rate was preserved only in B. The duration of atrial fibrillation (AF) was shorter in B than in A and C (P < 0.05). The inducibility of AF tended to be lower, and the fibrillation cycle length was longer in B than in A and C. Conclusions: Oral verapamil started before but not after rapid atrial excitation prevents electrical remodeling. Verapamil may exert beneficial effects when it is taken during sinus rhythm, but not after more than 2 days of atrial tachyarrhythmia. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Arrhythmia (mechanisms); Atrial function; Ca-channel; Remodeling; Supraventr. arrhythmia

1. Introduction

Sustained atrial fibrillation (AF) has been shown to cause changes in atrial electrophysiological function that further promote the occurrence and persistence of AF. This is referred to as atrial electrical remodeling [1–3]. These progressive electrophysiological changes include shortening of atrial effective refractory period (ERP) with loss of rate adaptation, slowing of intra-atrial conduction velocity (CV), and increase in the inducibility and duration of AF. Clinical experience also suggests that AF is more difficult to convert and is more likely to recur when the duration of AF is prolonged.

Recent experimental studies have suggested that intracellular Ca overload appears to play a central role in the development of electrical remodeling resulting from prolonged rapid atrial excitation [4–6]. It has been demonstrated that intravenous administration of verapamil can prevent electrical remodeling induced by AF of several minutes or atrial tachycardia of several hours [5–10]. However, the long-term clinical efficacy of Ca channel blocking agents in treating AF remains controversial [11–14].

Verapamil is often prescribed during AF to slow ven-
tricular response. It is possible that the efficacy of this agent in preventing electrical remodeling may be diminished or even lost once intracellular Ca overload is established. The purpose of this study was to prove or disprove the hypothesis that if verapamil prevents Ca overload, its efficacy would be greater only when administered before, rather than after the commencement of rapid atrial excitation.

2. Methods

2.1. Animal preparation

The study protocol was approved by the institutional scientific review committee. For this study, we used 24 adult mongrel dogs weighing 13–25 kg. The dogs were anesthetized with pentobarbital sodium (20 mg/kg i.v.) and ketamine chloride (15 mg/kg i.v.), and were then intubated and ventilated at a rate of 10–12 breaths/min with a Harvard Apparatus Model 607 Ventilator. A right fifth intercostal thoracotomy was performed. The pericardium was opened and the heart suspended in a pericardial cradle. A custom-made electrode (Nihon Koden; Tokyo, Japan) was sutured to the right atrial appendage (RAA). This electrode contains three sets of bipoles with a 2 mm interpolar distance. The most distal bipole served for pacing, while the middle bipole located 8 mm proximally and the most proximal bipole with 15 mm interelectrode distance were used for recording. The electrode lead was tunneled subcutaneously to the back and connected to the pacemaker (Nihon Koden, Tokyo, Japan) in the jacket. The pacemaker was programmed to provide rapid pacing at 400 ppm [15]. This rate was maintained, except for a brief period for measurement of electrophysiological parameters. All dogs were given oral antibiotics during a 5-day recovery period.

2.2. Study groups

The 24 dogs were divided into three groups (Fig. 1). In eight dogs, 2 days after rapid atrial pacing at 400 ppm was started, daily administration of verapamil (8 mg/kg per day) was initiated (After group; A). In another eight dogs, oral verapamil was started 1 week before the start of rapid pacing (Before group; B). In the remaining eight dogs, only rapid atrial pacing was started, without verapamil administration (Control group; C).

2.3. Electrophysiological measurements

All electrophysiological parameters were obtained after pharmacological autonomic blockade with intravenous atropine (0.04 mg/kg) and propranolol (0.2 mg/kg) [16]. In all of the study group dogs, we measured the atrial effective refractory period (ERP) and conduction velocity (CV) at basic cycle lengths (BCLs) of 200 and 300 ms on the day before (P0), and 2(P2), 7(P7), 14(P14) days after the commencement of rapid pacing. Among group B dogs, the ECG and electrophysiological parameters were measured both before (Pre-V) and 1 week after the start of verapamil oral administration (P0). On each study day, the measurement was performed 6–8 h after the dose of verapamil was administered to the group A or B dogs. The ERP was measured by applying eight basic (S1) stimuli followed by a premature stimulus (S2) with the coupling S1S2 interval decreased in 2-ms steps, until capture no longer occurred. The ERP was defined as the longest S1S2

![Fig. 1. The study protocol. In the control group (group C), following a 5-day recovery period after surgery, only continuous rapid atrial pacing at 400 ppm was started. In the after group (group A), oral verapamil was administered 2 days after the commencement of rapid atrial pacing. In the before group (group B), oral verapamil was started 1 week before the initiation of rapid atrial pacing.](https://academic.oup.com/cardiovascres/article-abstract/54/2/447/275605)
interval failing to produce a response. The ERP was obtained three times for each BCL, and the mean ERP values were used for data analysis. All basic and premature stimulations were performed using square impulses of 2-ms duration and an intensity four times the excitability threshold. The degree of rate adaptation was defined according to Attuel et al. [17] and Pandozi et al. [18].

Briefly, the slope value was calculated by dividing the difference of two ERPs by the difference of corresponding BCLs. The CV was calculated based on the conduction time recorded between the two recording electrodes 15-mm apart implanted in the RAA during basic pacing from the distal electrode. The WL was calculated by multiplying ERP and CV [19]. All electrophysiological data were obtained using a pacing stimulation unit (Cardiac Stimulator BC-02A; Fukuda Denshi, Tokyo, Japan; Pulse Generator 88-1346; Nihon Koden, Tokyo, Japan; and Isolator ss-202J; Nihon Koden). Blood pressure was measured by a catheter inserted into the right femoral artery. The standard surface electrocardiogram, arterial blood pressure, atrial electrograms, and stimulus signals were monitored and stored in the recorder (Polygraph system RM6000; Nihon Koden).

After obtaining baseline electrophysiological data, AF induction was attempted using 50 Hz, 2 ms burst stimuli from the pacing electrode at four times the diastolic threshold. AF was defined as a rapid (>300/min) irregular atrial rhythm with varying atrial electrogram morphology. We averaged 10 consecutive cycle lengths of atrial activation after stabilization of AF by measuring the peak to peak interval for each signal to obtain the FF interval.

2.4. Daily oral administration of verapamil

Verapamil was administered orally 8 mg/kg per day in two divided doses. The concentrations of verapamil, and its metabolite, norverapamil, were determined just before each electrophysiological study.

To evaluate the clinical effects of verapamil, we measured the heart rate and the blood pressure, as well as the Wenckebach point and the 2:1 point of atrioventricular conduction, which were determined by continuous atrial pacing with the cycle length (CL) decremented in steps of 10 ms. The longest pacing CL at which 1:1 AV nodal conduction failed was taken as the Wenckebach point. The PR(PQ), QRS duration, QT, and RR intervals were also measured from the surface ECG recording. All parameters were obtained after pharmacological autonomic blockade with intravenous atropine and propranolol.

2.5. Statistical analysis

Average data is presented as mean±S.E.M. Paired data were compared using the Student’s t-test. To evaluate differences between groups of discrete variables, a two-tailed Fisher’s exact test was used. Time series data were analyzed by repeated-measured ANOVA, followed by a Bonferroni method. A corrected $P<0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the three groups were not significantly different with respect to body weight, ERP, CV, WL, and AF inducibility. Nor did the mean diastolic excitability threshold differ among the groups, remaining unchanged throughout the study (Table 1).

3.2. Effects of verapamil on ECG and electrophysiological parameters

Verapamil slightly and insignificantly slowed the heart rate and decreased the blood pressure (Table 2). The sinus CL increased from 405 to 414 ms, while blood pressure decreased from 176 to 168 Torr. The PR interval on the surface ECG was significantly prolonged from 92 to 108 ms following the administration of verapamil. Verapamil also increased the Wenckebach point from 200 to 230 ms, and the longest CL resulting in 2:1 AV block also increased from 170 to 200 ms ($P<0.05$ vs. Pre V). These effects were maintained throughout the study protocol.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average body weight (kg)</td>
<td>15.5±3.8</td>
<td>15.2±3.4</td>
<td>15.3±3.3</td>
<td>ns</td>
</tr>
<tr>
<td>RP(Q) interval (ms)</td>
<td>402±15</td>
<td>405±13</td>
<td>403±15</td>
<td>ns</td>
</tr>
<tr>
<td>PQ interval (ms)</td>
<td>92±13</td>
<td>94±15</td>
<td>95±13</td>
<td>ns</td>
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<tr>
<td>QTc interval</td>
<td>0.43±0.2</td>
<td>0.42±0.2</td>
<td>0.43±0.2</td>
<td>ns</td>
</tr>
<tr>
<td>ERP/BCL200 (ms)</td>
<td>115±8</td>
<td>113±9</td>
<td>116±11</td>
<td>ns</td>
</tr>
<tr>
<td>CV/BCL200 (cm/s)</td>
<td>83±12</td>
<td>85±15</td>
<td>84±11</td>
<td>ns</td>
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<tr>
<td>WL/BCL200 (cm)</td>
<td>9.5±0.9</td>
<td>9.6±0.8</td>
<td>9.7±0.4</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of AF (s)</td>
<td>1.5±3.5</td>
<td>1.8±2.5</td>
<td>1.4±2.6</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>176±15</td>
<td>168±22</td>
<td>177±19</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic threshold (mA)</td>
<td>1.5±0.8</td>
<td>1.8±0.6</td>
<td>1.4±0.9</td>
<td>ns</td>
</tr>
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</table>
Table 2
The electrophysiological changes before and after verapamil administration in group B dogs

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Verapamil*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus cycle length (ms)</td>
<td>405±26</td>
<td>414±35</td>
<td>ns</td>
</tr>
<tr>
<td>PR(Q) interval (ms)</td>
<td>92±13</td>
<td>108±15</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>51±6</td>
<td>50±5</td>
<td>ns</td>
</tr>
<tr>
<td>QTs interval</td>
<td>0.42±0.2</td>
<td>0.42±0.3</td>
<td>ns</td>
</tr>
<tr>
<td>ERP/200 ms (ms)</td>
<td>114±8</td>
<td>112±10</td>
<td>ns</td>
</tr>
<tr>
<td>ERP/300 ms (ms)</td>
<td>128±11</td>
<td>128±10</td>
<td>ns</td>
</tr>
<tr>
<td>Conduction velocity/200 ms (cm/s)</td>
<td>82±7</td>
<td>80±11</td>
<td>ns</td>
</tr>
<tr>
<td>Wenckebach point (ms)</td>
<td>200±5</td>
<td>230±8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>2:1 AV block point (ms)</td>
<td>170±11</td>
<td>200±13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Duration of AF (s)</td>
<td>1.5±3.5</td>
<td>1.8±2.5</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>176±15</td>
<td>168±22</td>
<td>ns</td>
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</tbody>
</table>

* Data are obtained after 7 days of verapamil administration before the start of rapid pacing.

QT interval did not change with verapamil administration. Before commencement of rapid atrial pacing, the agent exerted no statistically significant effects on the mean atrial ERP, the intra-atrial CV, or AF duration. The mean concentrations of verapamil at the time of each electrophysiological study were 34±17 μg/ml in group B, and 37±19 μg/ml in group A. And the mean concentrations of norverapamil were 63±12 μg/ml in group B, and 61±16 μg/ml in group A.

3.3. Time course of electrical remodeling off drug

Among group C dogs that were not administered verapamil, ERP in response to rapid atrial pacing decreased significantly, from 114 to 104 ms after 2 days of pacing (Fig. 2, P<0.05 vs. P0). ERP decreased even further at P7, but remained nearly unchanged thereafter. The CV slowed more gradually and progressively over the 14 days of pacing. The WL also shortened significantly at P7, this became even more pronounced at P14 (Figs. 3 and 4). These changes were similarly demonstrated with pacing CLs of 200 and 300 ms. In group C dogs, while the slope value was 0.15±0.04 at P0, it became significantly smaller at P2, P7, P14 (0.09±0.03, 0.07±0.04, 0.08±0.04, respectively; P<0.05), suggesting a reduction of rate adaptation of ERP.

3.4. Effects of verapamil on electrical remodeling

Notably, among the group B dogs with prior verapamil treatment, ERP and CV did not change during the 14 days of pacing, remaining above those for the group C dogs. The WL shortened less, and remained greater than that in the group C dogs (Figs. 2–4).

In contrast, among group A dogs, the changes in ERP, CV, and WL were similar to those in the group C dogs (Figs. 2–4).

Characteristically in group B dogs, the slope values were essentially unchanged throughout the study (0.16±0.05, 0.12±0.03, 0.11±0.04, 0.15±0.04 at P0, P2, P7, P14, respectively; P=ns), suggesting a preserved rate adaptation of ERP. In contrast, in group A dogs, the slope value was 0.17±0.05 at P0, which reduced significantly to 0.09±0.04, 0.08±0.04, 0.08±0.05 at P2, P7, P14, respectively (P<0.05).

3.5. AF inducibility, FF interval, and AF duration

AF lasting more than 15 s became inducible only after 7 days of rapid pacing in 33% at P7 and 42% at P14 in the group C dogs. Although complete prevention of AF was not possible in
Fig. 3. Temporal change of CV. In response to rapid pacing, CV slowed significantly at P7 in group C (□) and A dogs (∆). In contrast, in group B dogs (○), CV did not change during 14 days of pacing.

the group B dogs, induction tended to be less frequent, with FF intervals longer in group B than in group C (Fig. 5). Moreover, in the group B dogs with prior verapamil treatment, the duration of induced AF was significantly reduced compared to group C or A (P<0.05 vs. C, A) (Fig. 6).

4. Discussion

4.1. Major findings

Electrical remodeling in response to rapid atrial pacing was characteristically demonstrated among the control dogs not administered verapamil, in whom ERP decreased rapidly and significantly with a reduction of rate adaptation by P2, while CV and WL slowly and progressively decreased over the entire pacing period of 14 days. This phenomenon was also observed in the dogs with verapamil started after rapid atrial pacing. In contrast, in the verapamil pretreated dogs, ERP, CV, and WL did not change significantly during the 14 days of rapid atrial pacing and remained greater than in the control group and the after group dogs. The adaptation of ERP to rate was only preserved in the verapamil pretreated dogs. Although verapamil failed to prevent AF induction completely in
either group, AF induction tended to be less frequent, and FF intervals were longer preserved in the verapamil pretreated dogs than in the after group dogs. In addition, in the verapamil pretreated dogs, the duration of induced AF was significantly less than for the control dogs or the dogs with verapamil started after rapid atrial pacing. It was thus demonstrated that verapamil, if administered before but not after initiation of rapid atrial pacing, can at least partially prevent electrical remodeling in this experimental model.

4.2. Pretreatment with verapamil for prevention of electrical remodeling

Several studies have demonstrated that intravenous verapamil administration started before rapid pacing prevents or attenuates electrophysiological changes provoked by rapid pacing or pacing-induced AF.

Verapamil started 30 min [5], or 4 h [7] before the initiation of rapid atrial pacing, or before the induction of AF [8,9], successfully attenuated electrophysiological changes, especially ERP shortening. Goette et al. reported that while biopsy specimens from the atrium of the dogs subjected to rapid pacing without treatment of verapamil showed mitochondrial swelling consistent with Ca overload, tissues taken from the atrium of the verapamil-treated dogs were normal [5].

In accordance with these studies, our study demonstrated that verapamil helped to prevent electrical remodeling only when it was started before rapid pacing. However, significant discrepancies were found between the results of the present study and those reported by Lee et al. [20], who reported that verapamil was effective in preventing atrial electrical remodeling for as long as 1 day of rapid atrial pacing, but that this effect dissipated after 1 week of rapid pacing. As Ausma et al. recently reported [21], a number of sarcolemma-bound Ca deposits increased significantly after 1 and 2 weeks of AF, but then decreased at 4–8 weeks, and falling even below control level at 16 weeks, suggesting that this beneficial effect may not be permanent. There are, however, methodological differences between the studies by Lee et al. and us, which may account for the discrepancy. Unlike our study, Lee et al. not only used a lower dose of verapamil (5–6 mg/kg per day), but did not report on the plasma concentrations of verapamil and norverapamil, or their effects on hemo-
dynamic or electrocardiographic variables. Therefore, there is no direct or indirect evidence that the dose of verapamil was adequate in their study. Moreover, the acute intravenous administration of verapamil which was done by Lee et al. at the time of the electrophysiological study in addition to the daily oral dose, may have activated sympathetic adrenergic system, thereby leading to facilitation of conduction and shortening of the refractory period [22–26], which may have affected the results.

Another important difference is that Lee et al. created a complete AV block in the dogs studied, and paced the ventricle at a rate of 80 ppm—much slower than the physiological heart rate for dogs weighing an average of 25 kg, which could even be deleterious hemodynamically. This may give rise to biventricular hypertrophy [27,28] with the development of fibrosis in the atrial tissue which in turn can facilitate reentry without a change in the wavelength [29].

Fareh et al. [30] also reported on the effects of Ca channel blockers in preventing electrical remodeling in the canine atrium, finding that diltiazem, another Ca channel blocker, was not effective in preventing the development of atrial electrical remodeling in a canine rapid pacing model similar to ours. The recovery time from the L-type Ca channel is 2.2 s for diltiazem, compared to 14.8 s for verapamil. The longer recovery time for verapamil may provide a greater use-dependent block, which may account for the diverging efficacy of the two drugs. In addition, just like mibefradil which has also been reported to prevent pacing-induced electrical remodeling [31], verapamil belongs to the phenylalkylamine group of Ca channel blockers. Diltiazem, on the other hand, belongs to the benzothiazepin group. Although mibefradil is known to block T-type Ca current which is preserved during electrical remodeling and can contribute to Ca overload, since verapamil has no such an effect, this structural difference may not necessarily account for the diverging effects in preventing electrical remodeling between verapamil and diltiazem.

4.3 Verapamil started after rapid atrial excitation

Two clinical studies have suggested that intracellular Ca-lowering drugs administered during AF may facilitate the maintenance of sinus rhythm after cardioversion [11,12].

On the other hand, other studies indicate that when administered after the onset of persistent AF, verapamil actually facilitates, rather than prevents electrical remodeling in humans [14,32]. In a randomized study to compare the efficacy of verapamil versus digoxin in patients with persistent AF [13], these agents were started during AF and were continued even after the sinus rhythm was restored. In this study, there was no difference in the maintenance of sinus rhythm after cardioversion of persistent AF between the two treatment groups. A previous study from our group also supported this view [33]. In that clinical study, the atrial refractory period after electrical cardioversion for chronic AF did not differ between patients taking or not taking oral verapamil. Furthermore, the recovery from electrical remodeling was even delayed in patients treated with verapamil, compared to those without verapamil. It was speculated that shortening of atrial ERP was pronounced in the group with verapamil since this agent reduced $I_{Ca}$ further in a stage where $I_{Ca}$ had been already reduced by atrial electrical remodeling induced by sustained AF.

In our present experimental study, the effects of verapamil administered after 2 days of rapid pacing were significantly reduced, suggesting that intracellular Ca overload had been established by this time. Since Ca overload develops immediately after the onset of AF, it is important that verapamil should be started before sustained AF. The present study thus is important in signifying the timing of verapamil administration, which critically determines the beneficial efficacy of preventing electrical remodeling.

4.4 Limitations of the study

Verapamil has been reported to decrease the incidence and duration of secondary AF by attenuating ERP shortening [9]. However, in our study, although verapamil significantly prevented pacing-induced declines in ERP, CV, and WL, it failed to totally prevent AF induction. The reasons why unchanged WL is associated with increasing AF inducibility are unclear. Since the measurement of WL was obtained only from one site in the atrium, it may not represent the electrophysiologic milieu of the whole atria. Atrial tissue is not homogenous, and there are Ca dependent fibers in and around the areas of the sinus node and AV node whose conduction can be significantly depressed in response to verapamil. This could lead to shortening of the WL in certain areas while not affecting WL in other areas, and may help induction and prolongation of AF. Another potential explanation for increasing susceptibility to reentry without change in WL may be dilatation of the atrium. Owing to its negative inotropic effect, verapamil may promote dilatation of the atrium. Since we did not examine structural changes in our study, further evaluation will be required to clarify this issue.

4.5 Clinical implications

Verapamil is often prescribed for ventricular rate control of atrial tachyarrhythmias. However, according to the results of the present study, this approach may not prevent the development of atrial electrical remodeling. It would be important to administer this drug during convalescence in sinus rhythm to prevent potential later developments of atrial electrical remodeling once AF begins. In practice, patients are unlikely to be able to take oral verapamil daily.
before the occurrence of AF or other atrial tachyarhythmias. It would only be possible to start the dose once they have experienced the first episode of arrhythmia. Potential clinical benefits with this approach may result when AF is not chronic, but paroxysmal and self-terminating.

It is important to understand that this approach of earlier administration of verapamil may not prevent AF initiation, but may prevent its prolongation and thus prevent an increase in the risk of thromboembolic complications. Another potential benefit with this approach is that in the presence of verapamil, the antiarrhythmic efficacy of Na channel blockers may be retained, facilitating the termination of AF of significant duration, an effect that may otherwise be diminished [34,35].

5. Conclusions

The present study has demonstrated that only prior treatment with daily oral verapamil reduces the progression of electrical remodeling caused by 14 days of rapid atrial excitation. Verapamil may exert a salutary effect when adaptation of the atrial refractory period: its relationship to vulnerability. Int J Cardiol 1998;32:355–364. clarifies the clinical efficacy of this strategy.

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