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# Effect of Verapamil on Long-Term Tachycardia-Induced Atrial Electrical Remodeling

Shih-Huang Lee, MD; Wen-Chung Yu, MD; Jun-Jack Cheng, MD; Chi-Ren Hung, MD;  
Yu-An Ding, MD; Mau-Song Chang, MD; Shih-Ann Chen, MD

**Background**—The effect of verapamil on long-term tachycardia-induced atrial electrical remodeling has not been reported.

**Methods and Results**—Forty-eight dogs were randomly divided into verapamil and control groups. The dogs in the verapamil group received verapamil 120 mg every day, those in the control group did not receive verapamil. Atrial effective refractory period (AERP), inducibility of atrial fibrillation (AF), and duration of AF were assessed before and after complete atrioventricular junction ablation with 1-day, 1-week, or 6-week rapid atrial pacing (780 bpm). AERP shortening, AERP dispersion, AERP maladaptation, and inducibility of AF after 1-day pacing was significantly attenuated by verapamil. However, verapamil did not have any significant effect on these parameters in the dogs with 1-week or 6-week pacing. Verapamil did not have any significant effect on the conduction velocity in the dogs with 1-day, 1-week, or 6-week pacing. Before rapid atrial pacing, verapamil significantly prolonged the duration of AF. In the dogs with 1-day pacing, the duration of AF measured immediately after termination of pacing was similar between the control and verapamil groups. However, in the dogs with 1-week or 6-week pacing, the duration of AF after pacing was significantly longer in the verapamil group.

**Conclusions**—Verapamil cannot prevent long-term (1 and 6 weeks, respectively) tachycardia-induced changes of atrial electrophysiological properties. Furthermore, verapamil increases the duration of AF in the dogs either before or after long-term rapid atrial pacing. (*Circulation*. 2000;101:200-206.)

**Key Words:** tachycardia ■ electrophysiology ■ atrium

It has recently been demonstrated that prolonged episodes of atrial fibrillation (AF) induced shortening, maladaptation, and increased dispersion of atrial effective refractory period (AERP).<sup>1-8</sup> This effect results in shorter wavelengths for the multiple wavelets during AF.<sup>9-11</sup> Some studies have demonstrated that verapamil could attenuate short-term ( $\leq 24$  hours) tachycardia-induced shortening and maladaptation of AERP and reduce the inducibility of AF.<sup>4,5,12</sup> However, the effect of verapamil on long-term tachycardia-induced atrial electrical remodeling has not been reported. The purpose of this study was to assess the effect of verapamil on long-term tachycardia-induced atrial electrical remodeling.

## Methods

### Experimental Preparation

As described previously, all experiments were performed in accordance with the *Guidelines for Animal Research* in this institute.<sup>13,14</sup> Forty-eight mongrel dogs of either sex weighing 20 to 25 kg were randomly divided into 2 groups, with 3 subgroups in each. The dogs in the verapamil group were fed with slow-releasing verapamil (Knoll) 120 mg every day starting 2 weeks before the baseline study. The dogs in the control group did not receive verapamil. The

administration of oral verapamil in the verapamil group was continued to the end of this study.

All dogs were anesthetized with an intravenous injection of thiopentone sodium, 25 mg/kg, and the chest was opened through the right fifth intercostal space. A quadripolar electrode catheter (Mansfield, Boston Scientific) was inserted through left femoral vein and positioned in right atrium to record an atrial electrogram. An electrode array containing 2 electrodes (electrode diameter, 1.5 mm; interelectrode distance, 2 cm) was sutured to the area between the Bachmann's bundle and right atrium for measuring intra-atrial conduction velocity (Figure 1). During measurements of conduction velocity, we paced from the electrode positioned near right atrium appendage at a pacing cycle length of 350 ms for 30 s. The conduction velocity was calculated from the conduction time recorded at the electrode positioned near Bachmann's bundle. Seven bipolar pacing wires for measuring AERP were sutured to the right and left atria.

### Baseline Electrophysiological Study

Each dog was pretreated with atropine and propranolol (0.04 and 0.2 mg/kg, respectively) followed by maintenance infusion (0.007 and 0.04 mg · kg<sup>-1</sup> · h<sup>-1</sup>, respectively).<sup>15</sup> In the verapamil group, the dogs received verapamil (0.3 mg · kg<sup>-1</sup> · h<sup>-1</sup>) during the experimental period, and the dogs in the control group received a matching saline infusion.<sup>5,12</sup> AERP was measured by a decremental technique with 2-ms steps at pacing cycle lengths of 200 ms (PCL 200), 250 ms

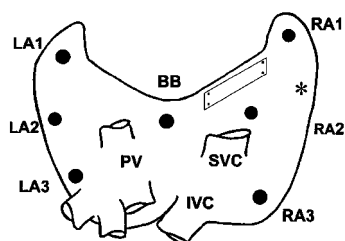
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From Shin Kong Wu Ho-Su Memorial Hospital, National Yang-Ming University (S.-H.L., J.-J.C., C.-R.H.), and Veterans General Hospital-Taipei (W.-C.Y., Y.-A.D., M.-S.C., S.-A.C.), Taiwan.

Correspondence to Shih-Ann Chen, MD, Division of Cardiology, Veterans General Hospital-Taipei, 201 Sec. 2, Shih-Pai Road, Taipei, Taiwan, ROC. E-mail sachen@vghtpe.gov.tw

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**Figure 1.** Locations of 7 pacing wires for measuring AERP (●), 1 electrode array for measuring intra-atrial conduction velocity, and 1 pacing lead for rapid atrial pacing (\*). BB indicates Bachmann's bundle; IVC, inferior vena cava; LA, left atrium; PV, pulmonary vein; RA, right atrium; and SVC, superior vena cava.

(PCL 250), and 350 ms (PCL 350) for 8 beats. AERP was defined as the longest S1-S2 coupling interval that failed to result in atrial capture. Basic pacing and extrastimulus were performed at twice diastolic threshold. The baseline ERP was determined 3 times and averaged. If AF occurred during AERP testing, it was cardioverted, and the dog was allowed to rest for 10 minutes. Then incremental S<sub>1</sub>S<sub>2</sub> from below the ERP were used. Dispersion of AERP was defined as the longest minus the shortest AERP at the same PCL of an individual heart.<sup>13,16</sup> Maladaptation of AERP was considered to be present if AERP failed to adapt or adapted reversely to change in heart rate.<sup>2,13,17,18</sup>

AF was defined as a rapid, irregular atrial rhythm with varying atrial electrogram morphology. The inducibility of AF was assessed by premature atrial stimulation during AERP testing. The duration of AF was assessed using atrial burst pacing with 50-HZ, 2-ms stimuli at 3 times the threshold current. If induced AF persisted >20 minutes, electrical cardioversion was performed and duration of AF was treated as 20 minutes in the calculation. To estimate mean AF duration, AF was induced 5 times for AF duration <10 minutes and twice for AF duration between 10 and 20 minutes. If AF lasted >20 minutes, no further AF induction was attempted.

### Electrophysiologic Study After Rapid Atrial Pacing

After baseline electrophysiological study, complete atrioventricular (AV) block was performed by radiofrequency ablation with a temperature control ablation catheter through the right femoral vein. In the 48 dogs used for this study, mean number of radiofrequency pulses required to create complete AV block was  $3 \pm 2$  (range, 1 to 7). Late recovery of AV nodal conduction did not occur in these dogs. After complete AV block was created by radiofrequency ablation, one unipolar epicardial pacing lead (Capsure, 4965, Medtronic) was sutured to right ventricular apex and connected to a programmable VVI pacemaker (Prevail 8086, Medtronic) in a subcutaneous pocket and set at 80 pulses per minute.<sup>3,13</sup> One unipolar epicardial pacing lead (Capsure, 4965, Medtronic) was sutured to right atrium (Figure 1); the lead was then connected to a pulse generator (Itrel 7425, Medtronic) implanted in a subcutaneous pocket and programmed to pace the atrium at 780 bpm with 2-ms pulses at 3 times threshold current. Atrial capture rates immediately after pacemaker implantation were  $449 \pm 52$  (range, 407 to 513) bpm. Then the atrial pacemaker was turned off. Seven pacing wires were tunneled subcutaneously to the right chest. After all the incisions were closed in layers, dogs were returned to animal quarters. One week later, the atrial pacemaker was started for both the control and verapamil groups. The surface EKG was checked every day to ensure constant pacing.

After 1-day, 1-week, or 6-week rapid atrial pacing, anesthesia was induced with thiopentone sodium (25 mg/kg) and homeostatic sheaths were inserted into right jugular vein and left femoral artery. A quadripolar electrode catheter was inserted through right jugular vein and positioned in right atrium to record an atrial electrogram. After intubation and mechanical ventilation, each dog was treated with atropine and propranolol (0.04 and 0.2 mg/kg, respectively)

followed by a maintenance infusion (0.007 and 0.04 mg · kg<sup>-1</sup> · h<sup>-1</sup>, respectively). In the verapamil group, the dogs received verapamil (0.3 mg · kg<sup>-1</sup> · h<sup>-1</sup>) during the experimental period, and the dogs in the control group received a matching saline infusion. Epicardial pacing wires used in the baseline study were exposed for AERP measurements. AERP was measured immediately and every 4 hours after termination of rapid atrial pacing, until the AERP returned within 4 ms of the baseline AERP. The inducibility and duration of AF were assessed using the same methods described in the baseline electrophysiological study. Surface ECG, temperature, blood pressure, arterial blood gas, sugar, and electrolyte levels were continuously monitored.

### Statistical Analysis

All continuous variables were expressed as mean ± SD. To evaluate differences between groups,  $\chi^2$  test with Yates' correction or Fisher's exact test was used to assess nonparametric data, and a Student's *t* test or Wilcoxon signed rank test was used for continuous variables. Time series were analyzed by a 2-way repeated measured ANOVA with Student-Newman-Keuls test. *P* < 0.05 was considered statistically significant.

### Results

Because values obtained with PCL 200, 250, and 350 ms showed similar statistical trend in all the atrial electrophysiological properties, only results obtained with the PCL 250 ms are presented.

#### Shortening of AERP After Pacing

In the control groups, AERP shortened significantly after termination of 1-day, 1-week, or 6-week rapid atrial pacing (Figure 2). The dogs with 6-week pacing showed the most significant shortening of AERP and it persisted for 24 hours. In the dogs with 1-day pacing, verapamil could prevent shortening of AERP, whereas, verapamil could not prevent shortening of AERP in the dogs with 1-week or 6-week pacing.

#### Dispersion of AERP After Pacing

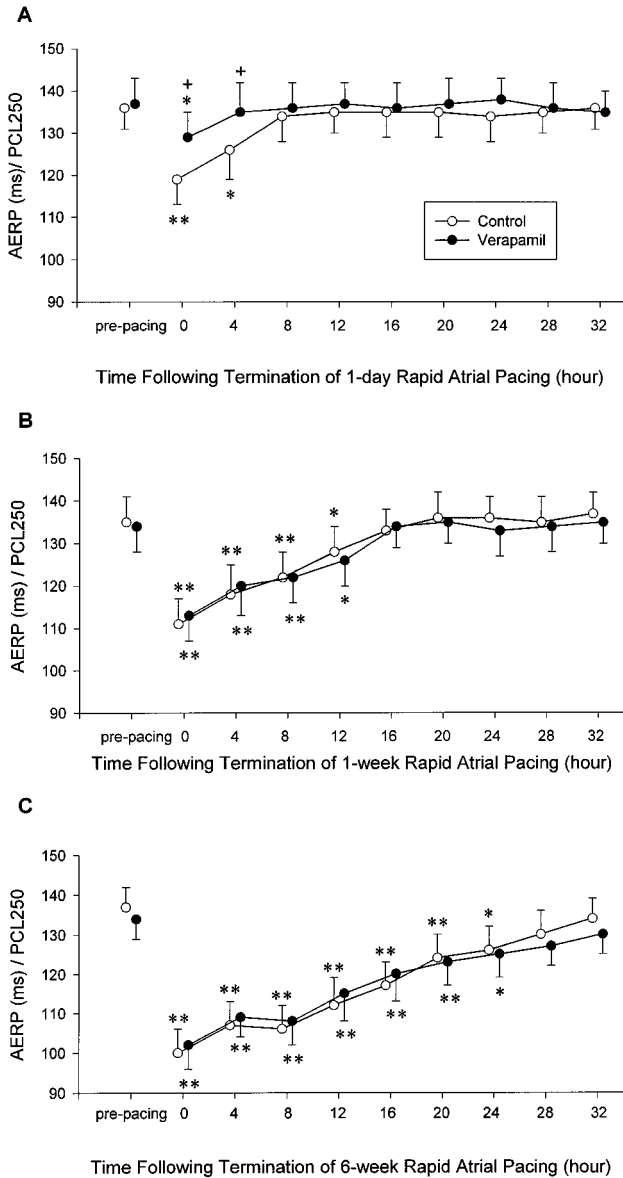
In the control groups, AERP dispersion increased significantly after termination of 1-day, 1-week, and 6-week rapid atrial pacing (Figure 3). The dogs with 6-week pacing showed the most significant increase of AERP dispersion and it persisted for 16 hours. In the dogs with 1-day pacing, verapamil could prevent the increase of AERP dispersion, whereas, verapamil could not prevent the increase of AERP dispersion in the dogs with 1-week or 6-week pacing.

#### Maladaptation of AERP After Pacing

In the control groups, incidence of AERP maladaptation increased significantly after termination of 1-day, 1-week, or 6-week rapid atrial pacing (Figure 4). The dogs with 6-week pacing showed the most significant increase in the incidence of AERP maladaptation and it persisted for 20 hours. In the dogs with 1-day pacing, verapamil could prevent the increased incidence of AERP maladaptation, whereas, verapamil could not prevent the increased incidence of AERP maladaptation in the dogs with 1-week or 6-week pacing.

#### Conduction Velocity After Pacing

In the control dogs with 1-day or 1-week pacing, conduction velocity was similar to that before pacing (Figure 5). However, in the dogs with 6-week pacing, conduction velocity

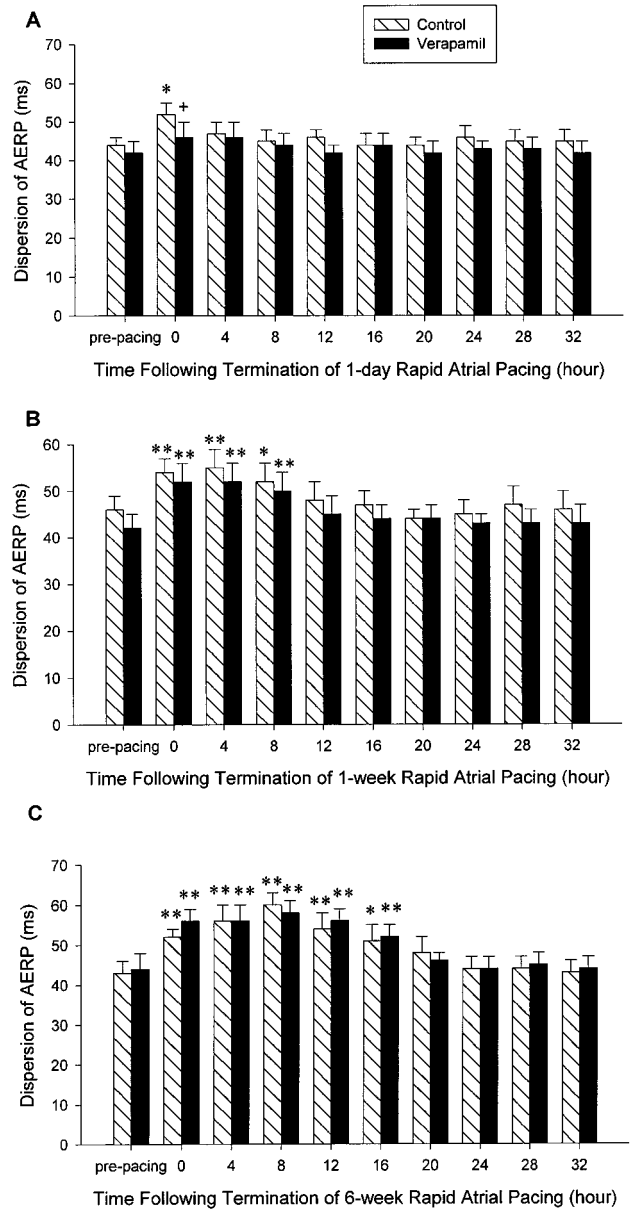


**Figure 2.** Verapamil significantly attenuated the AERP shortening induced by 1-day rapid atrial pacing (A). However, verapamil did not have any significant effect on AERP shortening after either 1-week (B) or 6-week (C) pacing. \*\* $P < 0.01$  vs prepacing; \* $P < 0.05$  vs prepacing; + $P < 0.05$  verapamil vs control group.

after pacing was significantly slower than that before pacing ( $P < 0.01$ ). In the dogs with 1-day, 1-week, or 6-week pacing, verapamil could not change conduction velocity significantly. Furthermore, in the dogs with 6-week pacing, the slower conduction velocity did not recover during the 32-hour follow-up in the control or verapamil group.

**Inducibility of AF After Pacing**

In the control groups, inducibility of AF increased significantly after termination of 1-day, 1-week, or 6-week rapid atrial pacing (Figure 6). The dogs with 6-week pacing showed the most significant increase in the inducibility of AF and it persisted for 24 hours. In the dogs with 1-day pacing, verapamil could prevent the increased inducibility of AF, whereas, verapamil could not prevent the increased inducibility of AF in the dogs with 1-week or 6-week pacing.



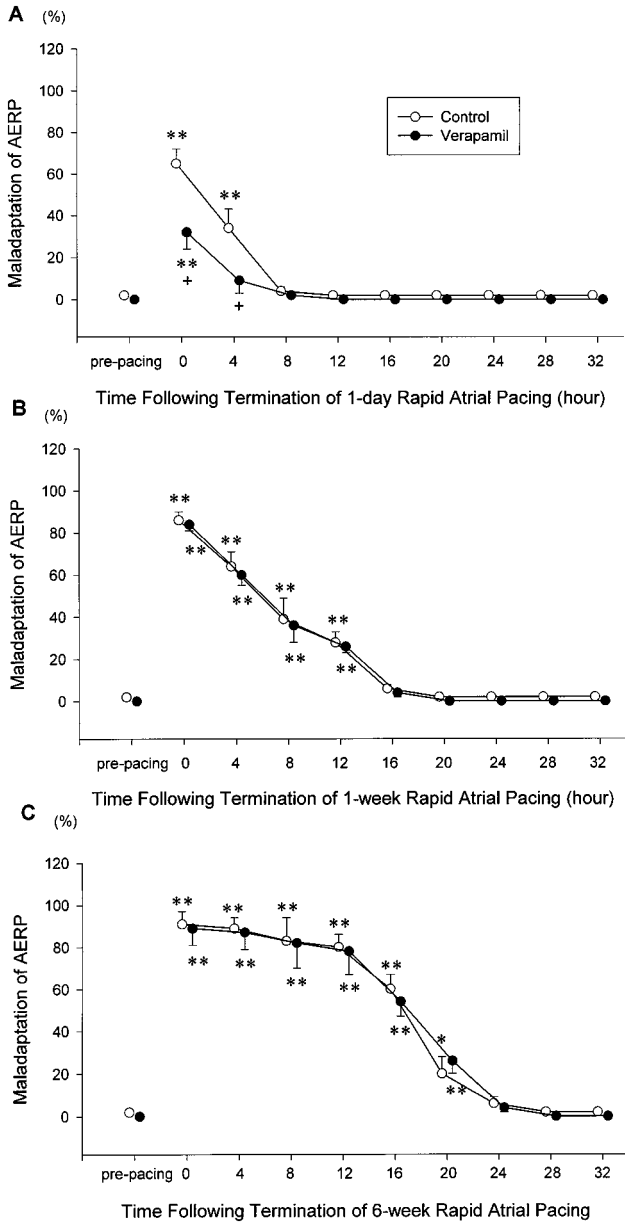
**Figure 3.** Verapamil significantly attenuated increased dispersion of AERP induced by 1-day rapid atrial pacing (A). However, verapamil did not have any significant effect on the dispersion of AERP after either 1-week (B) or 6-week (C) pacing. \*\* $P < 0.01$  vs prepacing; \* $P < 0.05$  vs prepacing; + $P < 0.05$  verapamil vs control group.

**Duration of AF After Pacing**

The duration of AF before pacing in the 3 verapamil subgroups was significantly longer than that in the control subgroups (Figure 7). In the dogs with 1-day pacing, the duration of AF measured immediately after termination of pacing was similar between the control and verapamil groups. However, in the dogs with 1-week or 6-week pacing, the duration of AF after pacing was significantly longer in the verapamil group.

**Discussion**

This study demonstrated that verapamil could not prevent long-term (1 and 6 weeks, respectively) tachycardia-induced

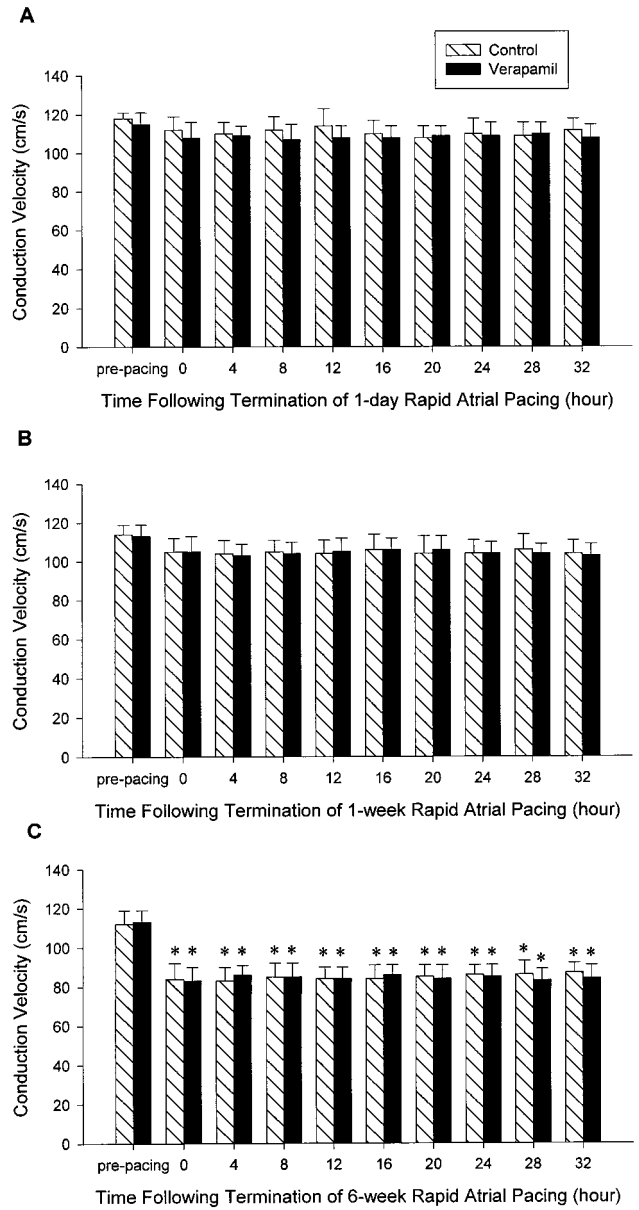


**Figure 4.** Verapamil significantly attenuated AERP maladaptation induced by 1-day rapid atrial pacing (A). However, verapamil did not have any significant effect on AERP maladaptation after either 1-week (B) or 6-week (C) pacing. \*\* $P < 0.01$  vs pre-pacing; \* $P < 0.05$  vs pre-pacing; + $P < 0.05$  verapamil vs control group.

changes of atrial electrophysiological properties, including shortening of AERP, increased dispersion and maladaptation of AERP, slower conduction velocity, and increased inducibility of AF. Furthermore, verapamil increased the duration of AF in the dogs either before or after long-term rapid atrial pacing.

**Effect of Verapamil on AERP**

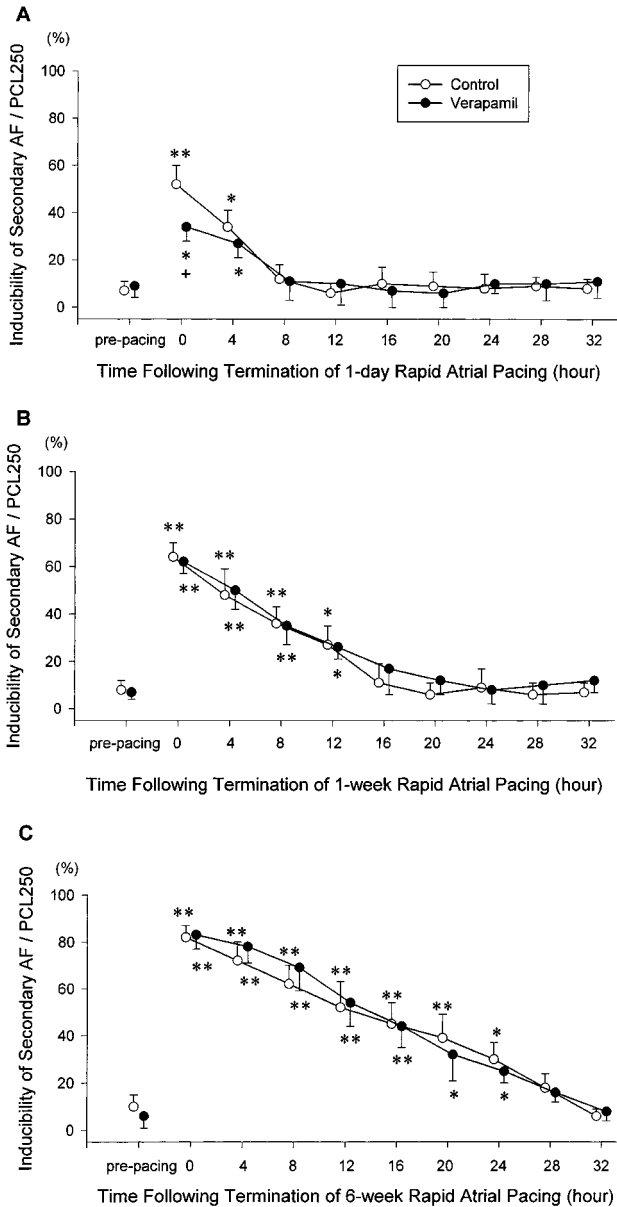
Goette et al demonstrated that 7 hours of pacing at 800 bpm in dogs significantly shortened the AERP by 12%, and that dogs pretreated with verapamil could prevent the AERP shortening induced by rapid pacing.<sup>4</sup> Tieleman et al found that shortening of goat AERP induced by 24-hour mainte-



**Figure 5.** Verapamil did not have any significant effect on conduction velocity after 1-day (A), 1-week (B), or 6-week (C) rapid atrial pacing. \* $P < 0.01$  vs pre-pacing.

nance of AF was significantly attenuated by verapamil.<sup>5</sup> Daoud et al demonstrated that in humans pretreatment with verapamil markedly attenuated short-duration ( $5.6 \pm 3.9$  minutes) AF-induced AERP shortening.<sup>12</sup> Consistent with these studies, the present study showed that verapamil attenuated the AERP shortening induced by 1-day rapid atrial pacing. However, verapamil did not attenuate the AERP shortening induced by long-term ( $\geq 1$  week) rapid atrial pacing.

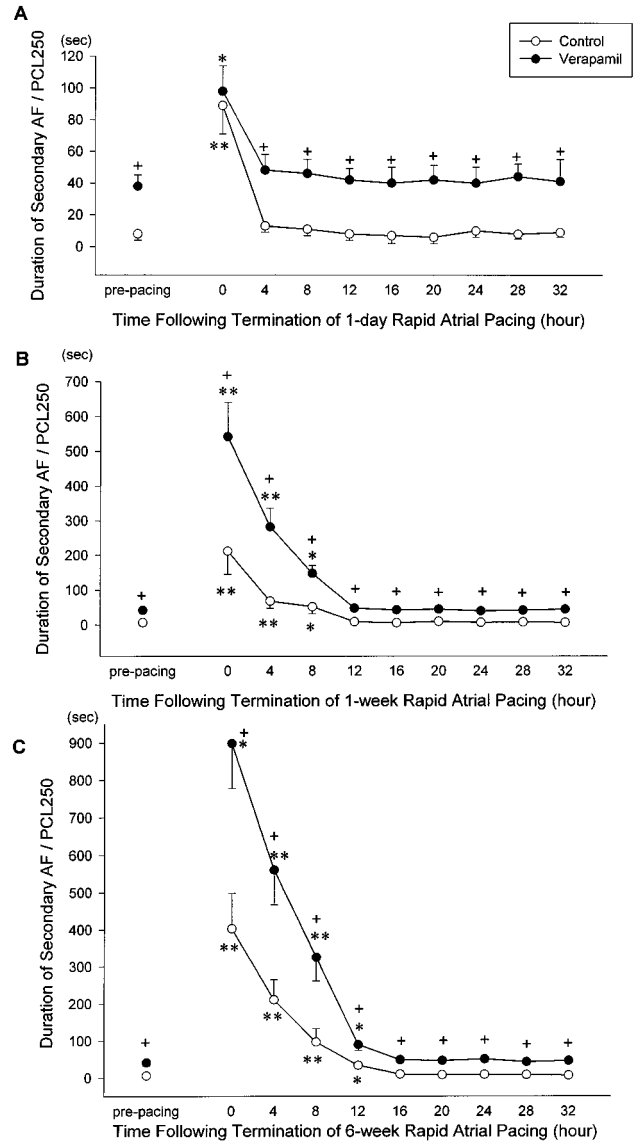
Animal studies have shown that AF is based on multiple wavelet reentry.<sup>19</sup> During AF, many independent wavelets might propagate in an ever-changing pattern around continuously shifting areas of conduction block. Dispersion of refractoriness was considered to favor induction and maintenance of reentrant arrhythmias.<sup>20,21</sup> The present study first showed that verapamil attenuated the AERP dispersion in-



**Figure 6.** Verapamil significantly reduced the increased inducibility of AF induced by 1-day rapid atrial pacing (A). However, verapamil did not have any significant effect on inducibility of AF after either 1-week (B) or 6-week (C) pacing. \*\* $P < 0.01$  vs pre-pacing; \* $P < 0.05$  vs pre-pacing; + $P < 0.05$  verapamil vs control group.

duced by 1-day rapid atrial pacing; however, verapamil did not attenuate the AERP dispersion induced by long-term rapid atrial pacing.

Attuel et al found that maladaptation of AERP might be a marker of atrial pathology causing a propensity to AF.<sup>17</sup> Le Heuzey et al measured the effect of heart rate on action potential recorded from isolated strips of human atrial myocardium, and they suggested that maladaptation of AERP might be the cause of AF in humans.<sup>18</sup> However, Wijffels et al demonstrated that maladaptation of AERP was actually a consequence of AF in the goat model.<sup>2</sup> Tieleman et al showed that verapamil significantly attenuated the maladaptation of AERP induced by 24-hour maintenance of AF.<sup>5</sup> We first



**Figure 7.** Verapamil significantly prolonged duration of AF before rapid atrial pacing. In dogs with 1-day pacing, duration of AF measured immediately after termination of pacing was similar between the 2 groups (A). In dogs with 1-week or 6-week pacing, duration of AF was significantly longer in the verapamil group (B and C). \*\* $P < 0.01$  vs pre-pacing; \* $P < 0.05$  vs pre-pacing; + $P < 0.05$  verapamil vs control group.

demonstrated that pretreatment with verapamil could not prevent long-term tachycardia-induced maladaptation of AERP.

### Effect of Verapamil on Conduction Velocity

Depression of atrial conduction in the dogs with 6-week rapid atrial pacing could be related to the structural abnormalities documented by light and electron microscopy.<sup>1,22</sup> A recent study showed significant changes of connexin expression in goats with AF-induced remodeling; this finding suggested a potential role for intercellular coupling changes in altering conduction velocity.<sup>23</sup> Gaspo et al also demonstrated that atrial myocytes of rapidly paced dogs had reduced  $I_{Na}$ , possibly accounting for changes of conduction velocity.<sup>24</sup>

However, studies about the atrial conduction properties were not consistent. Wijffels et al showed no change of atrial conduction velocity in goat model; Elvan et al, Gaspo et al, and the present study showed decrease of conduction velocity in chronic dog model.<sup>2,3,7</sup> These divergent results might be due to the different duration of rapid pacing or fibrillation; the duration of pacing in Elvan's, Gaspo's and the present studies was longer than that of Wijffels'. The depressed conduction properties after 6-week rapid atrial pacing did not show evidence of recovery during the 32-hour follow-up. It might be an irreversible change, but we could not rule out a late recovery. Furthermore, the present study showed that verapamil did not have any significant effect on the conduction velocity either before or after rapid atrial pacing.

### Effect of Verapamil on Inducibility and Duration of AF

The shortening of AERP and depressed atrial conduction properties could lead to a shorter wavelength and increase the inducibility and duration of AF.<sup>9–11</sup> Consistent with Wijffels' study, we found that verapamil attenuated 1-day tachycardia-induced AERP shortening and reduced the inducibility of AF.<sup>5</sup> However, verapamil did not reduce the inducibility of AF after long-term rapid atrial pacing.

Although verapamil attenuated the shortening of AERP induced by 1-day rapid atrial pacing, the duration of AF measured immediately after rapid atrial pacing was similar between the control and verapamil groups. Furthermore, verapamil increased the duration of AF either before or after long-term rapid atrial pacing. An increase in the duration of electrically induced episodes of AF by verapamil has been reported. Shenasa et al showed that both intravenously and orally administered verapamil increased the duration of electrically induced AF, especially in patients with spontaneous paroxysmal AF.<sup>25</sup> Isomoto et al also reported that the duration of AF was increased after intravenous verapamil in patients with paroxysmal supraventricular tachycardia.<sup>26</sup> Previous studies have shown that verapamil has no significant effect on AERP.<sup>26–28</sup> The effect of verapamil on conduction velocity was controversial. Kumagai et al reported that verapamil increased intra-atrial conduction delay and fragmented atrial activity in patients with paroxysmal AF; this effect of verapamil would favor the maintenance of electrically induced AF.<sup>28</sup> However, Tieleman et al did not find any significant change in the conduction velocity at the Bachmann's bundle after verapamil administration in the goat model.<sup>5</sup> The present study showed a similar result.

### Study Limitations

First, only 7 pairs of electrodes were used in this study; a detailed atrial mapping using computerized multielectrode mapping is absent. However, this study still could provide clear concept about the effect of verapamil on AERP, conduction velocity, and AF. Second, although previous studies and this laboratory also showed that anisotropy, conduction velocities in different directions, and different atrial structures are relevant to occurrence of AF, these issues are beyond the scope of this study.<sup>29–31</sup> Third, whether the decrease in conduction velocity was related to structural

changes in the geometry of the atrium needs further study. Fourth, secondary AF induced during measurements might affect recovery course of tachycardia-induced changes of atrial electrophysiological properties. Fifth, this study clearly showed that there were differences between the effects of verapamil on short-duration and long-term tachycardia-induced changes of atrial electrophysiological properties. However, mechanisms leading to the differences and extrapolation to human AF need further study.

### Clinical Implications

Verapamil is widely used for control of ventricular rate of AF. However, verapamil has no significant effect on the conversion of AF or maintenance of sinus rhythm.<sup>25,32,33</sup> The present study shows that if AF lasts for >1 week, verapamil cannot prevent the changes of atrial electrophysiological properties. Furthermore, verapamil may have a potential effect to increase the duration of AF, even when verapamil is initiated before onset of AF.

### Acknowledgments

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