EFFECTS OF INTRAVENOUS VERAPAMIL ON ATRIAL VULNERABILITY

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To investigate the effects of verapamil on indicators of atrial vulnerability, we examined 30 patients with paroxysmal supraventricular tachycardia who received intravenous verapamil during an electrophysiologic study. Single atrial extrastimuli were given before and after intravenous administration of verapamil to induce repetitive atrial firing (RAF) or atrial fibrillation, and to examine the maximum $A_2/A_1$, which was defined as the maximum ratio of the duration of the atrial electrogram resulting from premature stimulation ($A_2$) to that resulting from the basic drive beat ($A_1$). The maximum $A_2/A_1$ increased from $145\pm20\%$ to $154\pm25\%$ ($p<0.02$) after verapamil administration. The maximum $A_2/A_1$ in patients in whom neither RAF nor atrial fibrillation were induced both before and after verapamil were smaller than those in patients in whom RAF was induced only after verapamil (before; $138\pm20\%$ vs $165\pm15\%$, $p<0.02$, after; $144\pm22\%$ vs $172\pm17\%$, $p<0.05$). RAF or atrial fibrillation was induced only after verapamil in 6 patients, who showed a maximum $A_2/A_1$ before verapamil of $150\%$ or more. These data suggest that verapamil may induce repetitive atrial firing and possibly atrial fibrillation in some predisposed patients, especially in those that have a greater maximum $A_2/A_1$, which may be an indicator of local intraatrial conduction delay before drug infusion.

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VERAPAMIL, a slow calcium channel blocking drug, is frequently used to treat atrial fibrillation with rapid ventricular response. However, it may not be effective in terminating atrial fibrillation. The rate of conversion of paroxysmal atrial fibrillation to sinus rhythm with intravenous verapamil has been less than 15% in recent studies. Although previous reports have shown that verapamil administration induces atrial fibrillation in some patients who do not have a history of this arrhythmia, the effects of verapamil on the electrophysiologic properties of the atrial muscle, so-called atrial vulnerability, are still not clear.

Earlier clinical studies have demonstrated that repetitive atrial firing and fragmented atrial activity induced by programmed atrial stimulation are common in patients with paroxysmal atrial fibrillation, and these conditions have been used as electrophysiologic indicators of atrial vulnerability. Electrophysiologic studies have made it possible to evaluate the effect of antiarrhythmic agents on atrial vulnerability. Some investigators have evaluated the effects of flecainide or disopyramide. However,
little is known about the effects of verapamil on electrophysiological properties of the atrial muscle. The purposes of this report are (1) to investigate the effects of verapamil on electrophysiological indicators of atrial vulnerability, and (2) to clarify how verapamil influences the initiation and maintenance of repetitive atrial firing.

PATIENTS AND METHODS

Patients

Thirty patients with paroxysmal supraventricular tachycardia who received intravenous verapamil during an electrophysiologic study were included in this investigation. Informed consent was obtained from all patients. Twelve patients had atrioventricular reciprocating tachycardia, 16 patients had atrioventricular nodal reentrant tachycardia, and 2 patients had intraatrial reentrant tachycardia. One of the patients with atrioventricular nodal reentrant tachycardia had a history of transient atrial fibrillation. There were 16 men and 14 women who ranged in age from 13 to 80 years (mean 53 ± 18). None of the patients had a history of cardiac surgery or any clinical evidence of valvular heart disease, ischemic heart disease, or cardiomyopathies. Chamber dimensions and functions were normal in the echocardiographic study in all patients.

Stimulation Protocol

No cardioactive medications were given to the patients for at least 72 h before the study. Stimulation and recordings were performed using 6F bipolar or quadripolar catheters (USCI) with an interelectrode distance of 1 cm. The recording catheters were inserted via the antecubital, subclavian or femoral veins, and were positioned in the high lateral right atrium and His bundle area. Atrial electrograms were filtered at 50 to 1000 Hz and recorded with a Siemens-Elema Mingograph 800 at a paper speed of 100 mm/sec. Atrial stimulation was performed from the distal electrode of the quadripolar catheter positioned at the right atrial appendage at twice the diastolic threshold with a duration of 2 msec using a cardiac stimulator (Nihon Koden SEC-2102).

A single premature stimulation was given immediately after 8 basic stimuli with a cycle length of either 500 msec (23 patients) or 700 msec (7 patients). The coupling interval of the premature stimulation was decreased by 10 msec steps until the effective refractory period of the atrium was reached.

Drug Administration

After the control study was completed, verapamil, 0.1 mg/kg body weight, was administered intravenously for 5 min while blood pressure was monitored. Five minutes after completion of the infusion, the electrophysiologic studies were repeated. The basic cycle length remained unchanged before and after drug administration. Pacing studies were completed within 20 min.
Fig. 2. Case No 30. A) Before verapamil administration, a single premature stimulation with a coupling interval of 210 msec prolonged the duration of the HLRA electrogram from 70 to 105 msec, and repetitive atrial firing was induced. B) After verapamil administration, the duration of the HLRA electrogram increased from 90 to 170 msec at the same coupling interval as that before verapamil, and repetitive atrial firing was induced and maintained. aVF, V1 = scalar electrographic leads. HLRA = high lateral right atrium. RAA = right atrial appendage. HBE = His bundle electrogram. A1 = duration of the HLRA electrogram at the basic stimulation. A2 = duration of the HLRA electrogram at the atrial premature stimulation.

Definitions
Repetitive atrial firing was defined as the occurrence of 2 or more successive atrial electrograms induced by a single premature stimulation. Atrial fibrillation was defined as the appearance of rapid irregular atrial activity which lasted for more than 30 min.

A1 and A2 referred to the high lateral right atrial electrogram at the basic drive beat and at the premature stimulation, respectively. The maximum A2/A1 was defined as the maximum ratio of the duration of the atrial electrogram resulting from the premature stimulation (A2) to that resulting from the basic drive beat (A1) (Figs. 1 and 2).

The effective refractory period of the atrium was defined as the longest coupling interval at which premature stimulation failed to result in atrial depolarization.

Statistical Analysis
Results are expressed as the mean ± standard deviation. Statistical significance was analyzed using the paired or non-paired t-test, and the difference between the proportions was compared using the chi-square test.

RESULTS
Clinical and electrophysiological data of the 30 patients are shown in Table I.

Classification of the Patients
The patients were divided into 4 groups based on the occurrence of repetitive atrial firing and atrial fibrillation before and after verapamil administration. Group I consisted
TABLE I CLINICAL AND ELECTROPHYSIOLOGICAL DATA

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of 19 patients in whom neither repetitive atrial firing nor atrial fibrillation was induced both before and after verapamil administration. Group II consisted of 5 patients in whom repetitive atrial firing was induced both before and after the infusion. Group III consisted of 4 patients in whom repetitive atrial firing was induced only after administration of verapamil. Group IV consisted of 2 patients in whom repetitive atrial firing was induced before administration of verapamil, and which lasted for more than 30 min after verapamil administration. These 4 patterns of the occurrence of repetitive atrial firing and atrial fibrillation accounted for all of the patterns seen in the 30 subjects (Fig. 3).

Duration of the Local Atrial Electrogram

The maximum A2/A1 was prolonged from 145±20% to 154±25% (p<0.02) after verapamil administration in the 30 patients: from 138±20% to 144±22% in group I, from 154±11% to 160±24% in group II, from 165±15% to 172±17% in group III, and from 152±2% to 197±12% in group IV. The maximum A2/A1 in group III was greater than that in group I both before and after verapamil (before; p<0.02, after; p<0.05)
Verapamil and Atrial Vulnerability

Control

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Fig. 3. Effects of verapamil on initiation of repetitive atrial firing (RAF) and atrial fibrillation (AF).

(Table II).

Repetitive Atrial Firing

The incidence of repetitive atrial firing increased from 23% to 37% after verapamil administration, but this change was not significant. The longest coupling interval that gave rise to repetitive atrial firing increased in 3 patients (Nos. 21, 23, and 29) after verapamil administration, but decreased in none of the 7 patients (group II and group IV) with repetitive atrial firing or atrial fibrillation both before and after verapamil administration.

The Effective Refractory Period of the Atrium

The effective refractory period of the atrium was 204 ± 31 msec before and 205 ± 31 msec after verapamil administration (difference not significant) in the 28 patients in groups I—III. In group IV, atrial fibrillation was sustained after verapamil administration, and an atrial effective refractory period could not be achieved. There was no significant difference in the effective refractory period of the atrium before and after verapamil administration in each group (Table II).

DISCUSSION

Effects of Verapamil on the Electrophysiological Properties of the Human Atrial Muscle

Atrial fibrillation has been induced when verapamil was administered intravenously during sinus rhythm and during paroxysmal supraventricular tachycardia. Gulamhusein et al. noticed that atrial fibrillation was induced by a single atrial stimulation after verapamil administration in patients with Wolff-Parkinson-White syndrome. Shenasa et al. showed that verapamil prolonged the duration of atrial fibrillation induced by electrical stimulation. The incidence of repetitive atrial firing and the longest coupling interval at which repetitive atrial firing was elicited in the present study increased, and atrial fibrillation was sustained in 2 patients after verapamil administration. These findings are consistent with previous observations of verapamil-induced atrial fibrillation and suggest that the atrial muscle is more vulnerable to this arrhythmia after verapamil administration in some patients.

It has been demonstrated that fragmentation and slowing of conduction in response to premature stimulation are associated with initiation of reentry. Previous studies have shown that the induction zone and the duration of the local atrial activity elicited by premature atrial stimulation are greater in patients with paroxysmal atrial fibrillation than in normal controls. Thus, the maximum A_2/A_1, which is an index of the duration of the local atrial activity, may be a marker of a substrate for intraatrial reentry, and may be used as indicator of predisposition to atrial fibrillation. Aizawa et al. showed that the prolongation of the local atrial activity that is elicited by premature atrial stimulation is augmented by verapamil administration. This finding is consistent with our results, and this prolongation was even more enhanced in groups of patients who showed a high maximum A_2/A_1 before verapamil administration. On the other hand, other previous experimental and clinical studies have shown that verapamil does not change intraatrial conduction time in subjects who do not have significant conduction disturbances. This latter finding is consistent with our observations in group I. Taken together, these findings suggest that patients who show prolongation of the local atrial activity that is elicited by premature atrial stimulation before verapamil infusion are prone to develop atrial fibrillation after administration of the drug.
TABLE II ELECTROPHYSIOLOGICAL CHANGES OF THE ATRIAL MUSCLE BEFORE AND AFTER ADMINISTRATION OF VERAPAMIL IN THE 4 GROUPS

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Abbreviations see Table I. **: p<0.02, *: p<0.05. 
+: ERP after verapamil in group IV could not be obtained due to induced sustained atrial fibrillation.

The Mechanism of the Initiation and Maintenance of Repetitive Atrial Firing by Verapamil

Ten Eick and Singer used microelectrode techniques to show that the atria of patients with P wave prolongation were hypopolarized when compared to atria of patients who did not have evidence of atrial diseases. This finding was consistent with that in dilated atrium and in the damaged His-Purkinje system and suggested the use of slow calcium channels instead of fast sodium channels in diseased tissues. We demonstrated that repetitive atrial firing was more easily induced and maintained after verapamil infusion in patients that had local conduction delay before drug administration. Therefore, the atria of these patients might use slow calcium channels, and the intra-atrial conduction delay which could permit the initiation and maintenance of atrial reentrant arrhythmias might be augmented by verapamil.

Other factors may contribute to the effects of verapamil on the electrophysiological properties of the atrial muscle. According to Moe et al, maintenance of atrial fibrillation depends on a short refractory period of the atrium. It is widely accepted that verapamil has no significant effect on the effective refractory period of the atrium, which agrees with our result. The duration of the local atrial electrogram that resulted from the premature stimulation was longer after verapamil administration than before administration, even with a uniform basic cycle length and coupling interval of the atrial stimulation in some patients (Fig. 2). Therefore, the present findings can hardly be explained based solely on atrial refractoriness.

The possibility of autonomic effects of verapamil should be entertained. Most hemodynamic studies suggest that clinical doses of verapamil cause peripheral vasodilation, leading to a sympathetic reflex. However, there is no evidence to support the supposition that a high state of adrenergic tone may result in initiation and maintenance of repetitive atrial firing. Nguyen et al demonstrated that isoproterenol infusion abolished the inducibility of repetitive atrial firing by reducing atrial latency and by decreasing the intraatrial conduction time. Therefore, it is difficult to explain the aggravation of atrial vulnerability based on the autonomic effects of verapamil.

Atrial dilatation is also a predisposing factor in the genesis of atrial fibrillation. In our patients, however, chamber dimensions and functions were normal as assessed by echocardiographic study.

Limitations

Only one of our patients had a history of atrial fibrillation. Further studies in patients with paroxysmal atrial fibrillation will be needed to confirm our findings. However, in the patient who did have a history of atrial fibrillation (No. 24), repetitive atrial firing was induced after verapamil infusion, but not before drug administration. Our results are further limited by the fact that the reproducibility of repetitive atrial firing and atrial fibrillation was not determined. Finally, the plasma concentration of verapamil was not obtained. Although we did not correlate electrophysiological effects of the drug with plasma levels, the doses used in the present study are considered to be within the therapeutic range.

Clinical Implications

Repetitive atrial firing and fragmented
atrial activity have been suggested to be indicators of a predisposition to atrial fibrillation. Our present study demonstrated that intravenous administration of verapamil increased the inducibility and persistence of repetitive atrial firing and augmented the fragmentation of the atrial activity in patients with baseline intraatrial conduction delay. Thus, intravenous verapamil may induce repetitive atrial firing and possibly atrial fibrillation in patients with sick sinus syndrome\textsuperscript{27}–\textsuperscript{29} dilatation of the atrium\textsuperscript{26} old age\textsuperscript{30} or a history of paroxysmal atrial fibrillation, since these patients are liable to possess intraatrial conduction delay.

REFERENCES


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