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 $145 \pm 20\%$ to $154 \pm 25\%$ ($p < 0.02$) 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; $138 \pm 20\%$ vs $165 \pm 15\%$, $p < 0.02$. after; $144 \pm 22\%$ vs $172 \pm 17\%$, $p < 0.05$). 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^{1,2}. Although previous reports have shown that verapamil administration induces atrial fibrillation in some patients who do not have a

history of this arrhythmia^{3–6} 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^{7–9}. 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^{10–12}. However,

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Fig.1. Measurements of the duration of the atrial electrogram. A single premature atrial stimulation (S2) with a coupling interval of 260 msec followed 8 successive basic stimulations (S1) with a cycle length of 500 msec. The duration of the HLRA electrogram was increased from 80 to 100 msec by a single premature stimulation. V1=scalar electrographic lead. HLRA=high lateral right atrium. A₁=duration of the HLRA electrogram at the basic stimulation. A₂=duration of the HLRA electrogram at the atrial premature stimulation.

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 stimulation³. 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 $\pm$ 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

	No	Age	PSVT	BCL (msec)	ERP (msec)		RAF zone (msec)		RAF duration		Max A_2/A_1 (%)	
					C	V	C	V	C	V	C	V
Group I	1	18	AVRT	500	180	180	none	none	none	none	145	154
	2	20	AVRT	500	180	190	none	none	none	none	144	138
	3	36	AVRT	500	200	190	none	none	none	none	127	133
	4	42	AVRT	700	190	210	none	none	none	none	156	121
	5	43	AVRT	700	240	220	none	none	none	none	122	155
	6	63	AVRT	500	190	200	none	none	none	none	129	129
	7	80	AVRT	500	190	240	none	none	none	none	157	131
	8	43	AVNRT	500	170	170	none	none	none	none	132	158
	9	46	AVNRT	500	170	170	none	none	none	none	168	183
	10	49	AVNRT	500	210	190	none	none	none	none	113	131
	11	49	AVNRT	500	200	190	none	none	none	none	113	124
	12	60	AVNRT	500	170	170	none	none	none	none	160	171
	13	66	AVNRT	500	200	170	none	none	none	none	110	129
	14	68	AVNRT	500	170	180	none	none	none	none	175	167
	15	73	AVNRT	500	250	260	none	none	none	none	135	120
	16	75	AVNRT	700	270	280	none	none	none	none	150	150
	17	75	AVNRT	500	240	220	none	none	none	none	131	173
	18	70	IART	500	250	250	none	none	none	none	140	169
	19	78	IART	700	240	250	none	none	none	none	109	108
Group II	20	61	AVRT	700	210	200	230–220	230–210	1 sec	1 sec	163	200
	21	66	AVRT	500	220	220	250–230	270–230	3 sec	1 sec	168	164
	22	32	AVNRT	500	170	180	230–180	230–190	3 sec	140 sec	144	150
	23	44	AVNRT	500	180	200	210–190	220–210	8 sec	8 sec	150	153
	24	64	AVNRT	500	170	190	210–180	210–200	1 sec	4 sec	144	135
Group III	25	13	AVRT	500	200	190	none	210–200	none	1 sec	150	152
	26	57	AVRT	500	190	200	none	230–210	none	1 sec	185	180
	27	37	AVNRT	500	170	150	none	200–160	none	10 sec	156	191
	28	59	AVNRT	700	260	240	none	260–250	none	2 sec	168	165
Group IV	29	54	AVRT	700	180	<230	230–190	240–230	92 sec	>30 min	150	205
	30	59	AVNRT	500	200	<210	230–210	230–210	6 sec	>30 min	153	188

PSVT: paroxysmal supraventricular tachycardia. AVRT: atrioventricular reciprocating tachycardia. AVNRT: atrioventricular nodal reentrant tachycardia. IART: intraatrial reentrant tachycardia. BCL: basic cycle length. ERP: effective refractory period of the atrium. RAF zone: coupling intervals giving rise to repetitive atrial firing (RAF). Max A_2/A_1 : maximum ratio of the atrial activity width at the premature stimulation to that at the basic stimulation. C: control. V: verapamil.

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 A_2/A_1 was prolonged from $145 \pm 20\%$ to $154 \pm 25\%$ ($p < 0.02$) after verapamil administration in the 30 patients: from $138 \pm 20\%$ to $144 \pm 22\%$ in group I, from $154 \pm 11\%$ to $160 \pm 24\%$ in group II, from $165 \pm 15\%$ to $172 \pm 17\%$ in group III, and from $152 \pm 2\%$ to $197 \pm 12\%$ in group IV. The maximum A_2/A_1 in group III was greater than that in group I both before and after verapamil (before; $p < 0.02$, after; $p < 0.05$)

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 rhythm³ and during paroxysmal supraventricular tachycardia^{4–5}. Gulamhussein et al noticed that atrial fibrillation was induced by a single atrial stimulation after verapamil administration in patients with Wolff-Parkinson-White syndrome⁶. Shenasa et al showed that verapamil prolonged the duration of atrial fibrillation induced by electrical stimulation¹³. 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^{6,13} 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 reentry¹⁴. 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^{8,9,15}. 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 administration¹⁶. 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^{17,18}. 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

	ERP (msec)		Max A ₂ /A ₁ (%)	
	C	V	C	V
Group I	207±32	209±34	138±20	144±22
Group II	190±23	198±15	154±11	160±24
Group III	205±39	195±37	165±15	172±17
Group IV	190±14	+	152±2	197±12

Abbreviations see Table I. **: $p < 0.02$, *: $p < 0.05$.

+: ERPs 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.¹⁹ This finding was consistent with that in dilated atrium²⁰ and in the damaged His-Purkinje system²¹ 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.²² It is widely accepted that verapamil has no significant effect on the effective refractory period of the atrium,^{17,23} 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.²⁴ 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.²⁵ 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.²⁶ 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;²⁷⁻²⁹ dilatation of the atrium;²⁶ old age;³⁰ or a history of paroxysmal atrial fibrillation, since these patients are liable to possess intraatrial conduction delay.

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