

Effects of β -Adrenergic Blockade on Verapamil-responsive and Verapamil-irresponsive Sustained Ventricular Tachycardias

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Abstract

To assess effects of β -adrenergic blockade on ventricular tachycardia (VT) of various mechanisms, electrophysiology studies were performed before and after intravenous infusion of propranolol (0.2 mg/kg) in 33 patients with chronic recurrent VT, who had previously been tested with intravenous verapamil (0.15 mg/kg followed by 0.005 mg/kg/min infusion). In the verapamil-irresponsive group, 10 patients (group IA) had VT that could be initiated by programmed ventricular extrastimulation and terminated by overdrive ventricular pacing, and 11 patients (group IB) had VT that could be provoked by isoproterenol infusion (3–8 μ g/min) but not by programmed electrical stimulation, and that could not be converted to a sustained sinus rhythm by overdrive ventricular pacing. Notably, in the group IA patients, all 10 patients had structural heart disease (coronary arteriosclerosis or idiopathic cardiomyopathy); β -adrenergic blockade accelerated the VT rate in one patient but exerted no effects on the VT rate in the remaining 9 patients, and VT remained inducible in all 10 patients. By contrast, in the group IB patients, 7 of the 11 patients had no apparent structural heart disease; β -adrenergic blockade completely suppressed the VT inducibility during isoproterenol infusion in all 11 patients. There were 12 patients with verapamil-responsive VT (group II). 11 of the 12 patients had no apparent structural heart disease. In these patients, the initiation of VT was related to attaining a critical range of cycle lengths during sinus, atrial-paced or ventricular-paced rhythm; β -adrenergic blockade could only slow the VT rate without suppressing its inducibility. Of note, 14 of the total 33 patients had exercise provokable VT: two in group IA, five in group IB, and seven in group II. Thus, mechanisms of VT vary among patients, and so do their pharmacologic responses. Although reentry, catecholamine-sensitive automaticity, and triggered activity related to delayed afterdepolarizations are merely speculative, results of this study indicate that β -adrenergic blockade is only specifically effective in a subset group (group IB) of patients with VT suggestive of catecholamine-sensitive automaticity.

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Introduction

β -Adrenergic blockade exerts a multitude of metabolic, hemodynamic, and electrophysiologic effects and has been shown to be clinically efficacious in the treatment of certain forms of ventricular tachyarrhythmias (1–4). However, the mechanisms by which β -adrenergic blockade suppresses ventricular tachyarrhythmias remain incompletely understood. In four patients with electrically inducible ventricular tachycardia (VT),¹ Wellens et al. (5) found that intravenous propranolol slowed the sinus rate but did not affect the VT rate and its inducibility. We and others (6–9), in contrast, observed that intravenous propranolol was effective in suppressing VT inducibility in patients in whom VT was provokable with intravenous infusion of isoproterenol. The disparity in responses to β -adrenergic blockade connotes that the occurrence of VT may be accounted for by different electrophysiologic mechanisms.

Using the technique of programmed electrical stimulation along with pharmacologic testing with intravenous verapamil, we have previously separated three “presumptive” mechanisms of VT in human beings: reentry, catecholamine-sensitive automaticity, and triggered activity related to delayed afterdepolarizations (10). In the present study, we assessed effects of β -adrenergic blockade on these three forms of VT. Our findings indicate that β -adrenergic blockade is only specifically effective in suppressing VT suggestive of catecholamine-sensitive automaticity.

Methods

Patients. Between July 1983 and July 1986, we studied 33 patients with clinically documented sustained VT that could be reproduced during the course of electrophysiologic evaluation. Sustained VT was defined as VT that lasted longer than 30 s. We excluded patients who were hemodynamically unstable and who had a prior history of congestive heart failure or who had an ejection fraction of < 40% as measured by radionuclide angiography (11). All 33 patients had had echocardiography and treadmill exercise testing using the standard Bruce protocol (12) before electrophysiology studies. Additionally, 24 patients had undergone cardiac catheterization with coronary angiography as clinically indicated. There were 22 men and 11 women ranging in ages from 18 to 66 (mean 42.5) yr (Tables I–III). 10 patients had arteriosclerotic heart disease with prior myocardial infarction of > 6 mo, 5 patients had idiopathic cardiomyopathy, and 18 patients had no clinical evidence of structural heart disease. All patients were clinically symptomatic with palpitations, dizziness, and/or syncope.

Plasma concentrations of catecholamines. In patients with VT provokable with treadmill exercise testing, blood samples were drawn for measurements of plasma epinephrine and norepinephrine levels

1. Abbreviations used in this paper: VT, ventricular tachycardia.

Table I. Clinical Profile of Group IA Patients with Verapamil-irresponsive Ventricular Tachycardia

Case No.	Sex/age		Cardiac diagnosis	Symptoms associated with VT	Duration	VT			TET provocability
						Rate	QRS pattern	QRS axis	
		yr			yr	beats/min			
1	M	42	ASHD/prior MI	Palpitations	2	170	RBBB	−120°	−
2	M	50	Cardiomyopathy	Palpitations	5	180	LBBB	−30°	−
3	M	66	ASHD/prior MI	Palpitations, syncope	6	200	RBBB	+130°	−
4	M	65	ASHD/prior MI	Dizziness	1.5	150	LBBB	+45°	+
5	M	58	Cardiomyopathy	Palpitations	3	200	RBBB	+60°	−
6	F	47	ASHD/prior MI	Palpitations	6	180	RBBB	+110°	−
7	M	56	ASHD/prior MI	Syncope	4	190	LBBB	+100°	−
8	F	65	ASHD/prior MI	Dizziness, syncope	7	170	RBBB	−30°	−
9	M	62	ASHD/prior MI	Palpitations	4.5	160	RBBB	−20°	+
10	M	64	ASHD/prior MI	Palpitations	5.5	170	RBBB	−30°	−

Abbreviations: ASHD, arteriosclerotic heart disease; LBBB, left bundle branch block pattern; MI, myocardial infarction; RBBB, right bundle branch block pattern; TET, treadmill exercise testing; VT, ventricular tachycardia.

through an indwelling intravenous cannula (heparin lock) in a standing position at rest and at the stage of treadmill exercise testing during which VT was provoked. The normal ranges for plasma epinephrine and norepinephrine levels in a standing position at rest as measured by the high-pressure liquid chromatography (13) were, respectively, 32 ± 9 and 256 ± 68 pg/ml.

Electrophysiology study. All patients gave informed consent, and all antiarrhythmic drugs were discontinued for at least five elimination half-lives before the study. The study was performed with patients in a postabsorptive, nonsedated state. With a conventional method (14), a quadripolar electrode catheter was introduced from the right femoral vein and placed in the right atrioventricular junction for recording the His bundle potential. Two additional quadripolar electrode catheters were also introduced from the right femoral vein and, respectively, placed in the high right atrium and the right ventricle for electrical stimulation and recording intracardiac electrograms. All intracardiac electrograms were simultaneously displayed with electrocardiographic leads I, II, and V₁ on a multichannel oscilloscopic recorder (DR-16;

Electronics for Medicine, White Plains, NY), and were recorded at a paper speed of 100 mm/s using filter frequency settings of 30–500 Hz.

A programmed digital stimulator (Bloom & Associates, Narberth, PA) was used to deliver electrical impulses of 2.0-ms duration at approximately twice diastolic threshold. During incremental pacing, the high right atrium and the right ventricle (apex and outflow tract) were, respectively, paced for 15–20 beats with abrupt cessation. We began pacing with a cycle length 20 ms shorter than that of the sinus rhythm. After each burst of pacing, we decreased the cycle length by 10–20 ms until the shortest pacing cycle length of 250 ms was reached.

During programmed extrastimulation, the high right atrium and the right ventricle (apex and outflow tract) were, respectively, driven at two cycle lengths ($S_1 - S_1$) (usually 600 and 400 ms). An atrial and a ventricular premature beat (S_2) were, respectively, introduced from late diastole at progressively shorter coupling interval ($S_1 - S_2$) after every eighth drive beat until effective atrial and ventricular refractory periods were, respectively, encountered. To increase the sensitivity of VT induction, timed double and triple ventricular premature beats (S_3

Table II. Clinical Profile of Group IB Patients with Verapamil-irresponsive Ventricular Tachycardia

Case No.	Sex/age		Cardiac diagnosis	Symptoms associated with VT	Duration	VT			TET provocability
						Rate	QRS pattern	QRS axis	
yr					yr	beats/min			
1	M	35	NAHD	Palpitations	3	150	LBBB	−20°	−
2	M	59	ASHD/prior MI	Palpitations, dizziness	12	200	LBBB	+90°	+
3	F	25	NAHD	Palpitations	5	160	LBBB	−60°	+
4	M	52	NAHD	Palpitations, dizziness	6	180	LBBB	+110°	−
5	M	56	Cardiomyopathy	Palpitations, syncope	3	170	RBBB	−10°	+
6	M	18	NAHD	Palpitations	1.5	190	LBBB	+130°	−
7	F	30	NAHD	Palpitations	2	210	LBBB	+120°	+
8	M	34	NAHD	Palpitations	0.5	170	LBBB	+50°	−
9	F	45	Cardiomyopathy	Palpitations	2	210	LBBB	+120°	+
10	M	45	NAHD	Palpitations	2	140	LBBB	−60°	−
11	M	60	ASHD/prior MI	Dizziness	5	180	LBBB	+120°	−

Abbreviations as in Table I. NAHD, no apparent heart disease.

Table III. Clinical Profile of Group II Patients with Verapamil-responsive Ventricular Tachycardia

Case no.	Sex/age	Cardiac diagnosis	Symptoms associated with VT	Duration	VT			
					Rate	QRS pattern	QRS axis	TET provocability
	yr			yr	beats/min			
1	F 20	NAHD	Palpitations, dizziness	0.5	190	RBBB	-45°	+
2	M 19	NAHD	Palpitations	1.5	90	RBBB	-75°	+
3	M 25	NAHD	Palpitations	3	120	LBBB	+45°	-
4	F 44	NAHD	Palpitations, dizziness	2.5	180	RBBB	-30°	-
5	F 48	NAHD	Palpitations, dizziness	20	160	RBBB	-60°	+
6	F 39	NAHD	Palpitations, dizziness	1	180	LBBB	+110°	+
7	M 18	NAHD	Palpitations	2.5	100	RBBB	-75°	-
8	M 29	NAHD	Palpitations	3	130	RBBB	-30°	+
9	F 36	NAHD	Palpitations, dizziness	5	170	LBBB	-60°	+
10	F 32	NAHD	Palpitations	1.5	145	LBBB	+90°	+
11	M 30	Cardiomyopathy	Palpitations	2	150	RBBB	-45°	-
12	M 28	NAHD	Palpitations	4	140	LBBB	+45°	-

Abbreviations as in Table I. NAHD, no apparent heart disease.

and S₄) were delivered if a single ventricular premature beat (S₂) failed to elicit VT during programmed ventricular extrastimulation. The protocol was continued until it provoked VT or until all extrastimuli (S₂, S₃, and S₄) failed to evoke ventricular responses. If programmed electrical stimulation failed to induce VT, isoproterenol was infused intravenously at graded dosage from 0.5 to 8 µg/min until VT emerged or the sinus rate was accelerated to a maximum of 150 beats/min (10). After the initiation of VT, we delivered short bursts of overdrive ventricular pacing in attempt to terminate the arrhythmia.

Pharmacologic testing. Pharmacologic testing with intravenous verapamil and intravenous propranolol were carried out on separate days (usually 3 d apart) in each patient. Electrophysiology study using the above described protocol was performed before and after administration of each drug. The dosage of intravenous verapamil was as previously described (10): 0.15 mg/kg of body weight over 2 min as a loading dose followed by continuous infusion at 0.005 mg/kg of body weight/min during which programmed electrical stimulation or isoproterenol infusion was repeated. The dosage of intravenous propranolol was chosen to achieve significant β -adrenergic blockade as recommended by Jose and Taylor (15): 0.2 mg/kg of body weight at 1 mg/min infusion rate. Programmed electrical stimulation or isoproterenol infusion was repeated 10 min later. In each patient, the time required to complete a repeat study was ~ 15–20 min. Results of responses to other antiarrhythmic agents were irrelevant to the present study and were, therefore, not included.

Classification of patients. We realized that results of basic electrophysiologic studies are difficult to be extrapolated to explain findings of intact human hearts, and that there are practical limitations of electrophysiology study techniques (10, 16, 17). Mechanisms of reentry, automaticity, and triggered activity related to delayed afterdepolarizations were applied (18–20) and patients were classified into two groups based on their responses to intravenous verapamil—verapamil-irresponsive (group I) and verapamil-responsive (group II).

Results

Before intravenous infusion of verapamil and propranolol, sustained VT with a QRS morphology identical to that occurred clinically could be reproduced during the control state in each patient. Among the 33 patients, intravenous verapamil

infusion exerted no effects on the inducibility of VT in 21 patients (group I: verapamil-irresponsive) and totally suppressed the VT inducibility in 12 patients (group II: verapamil-responsive).

Verapamil-irresponsive ventricular tachycardia (group I). Based on the modes of VT initiation and termination, they were subdivided into groups IA and IB. Group IA patients had electrically inducible VT and group IB patients had VT that could not be induced electrically but was provokable with intravenous infusion of isoproterenol.

There were 10 patients in group IA with ages ranging from 42 to 66 (mean 57.5) yr (Table I). All of them had apparent structural heart disease: eight had arteriosclerotic heart disease with prior myocardial infarction and two had idiopathic cardiomyopathy. During electrophysiology studies, incremental atrial pacing, atrial extrastimulation, and incremental ventricular pacing did not elicit VT in any of them. However, programmed ventricular extrastimulation provoked sustained monomorphic VT that could be terminated by overdrive ventricular pacing in all 10 patients (Fig. 1). In 4 of the 10 patients, the initiation of VT required only single ventricular extrastimuli. Of these four patients, the interval between the initiating ventricular premature beat and the first beat of VT was inversely related to the premature coupling interval of ventricular extrastimuli (Fig. 1). The rates of VT averaged 177 (150–200) beats/min, and QRS morphologies of VT were of a right bundle branch block pattern in seven patients and of a left bundle branch block pattern in three patients. In two patients (cases 4 and 9, Table I) treadmill exercise testing provoked the onset of VT. After intravenous infusion of propranolol (0.2 mg/kg), VT remained inducible in all 10 patients. One patient (case 8, Table I) manifested VT at a faster rate (increased from 170 to 220 beats/min) associated with symptomatic hypotension (blood pressure decreased from 110/70 to 70–80/50 mmHg) for which immediate overdrive ventricular pacing was necessary to terminate the arrhythmia. In the remaining 9 patients β -adrenergic blockade did not affect the cycle length of VT.

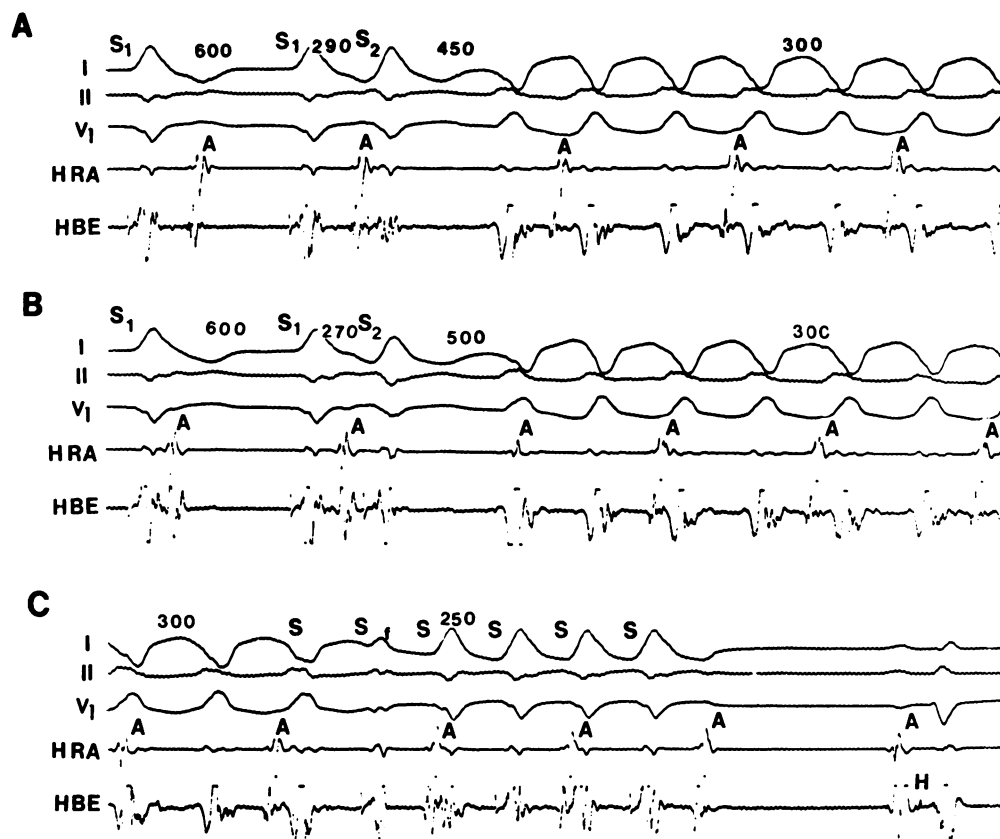


Figure 1. Induction of VT in the verapamil-irresponsive group (IA) with programmed ventricular extrastimulation (case 3, Table I). VT cannot be elicited by programmed atrial stimulation, but is readily inducible with programmed right ventricular extrastimulation. (A and B) The right ventricle is driven at a cycle length ($S_1 - S_1$) of 600 ms, ventricular premature beats (S_2) with premature coupling intervals of 290 and 270 ms, respectively, provoke an onset of sustained VT with a right bundle branch block pattern (axis $+130^\circ$), the cycle length of which is 300 ms. Note that the interval between the initiating ventricular premature beat and the first beat of VT is inversely related to the premature coupling interval of ventricular premature beats (S_2). (C) Overdrive right ventricular pacing at a cycle length of 250 ms easily terminates the arrhythmia. The VT remains inducible

and its cycle length remains unchanged after either intravenous verapamil or β -adrenergic blockade with intravenous propranolol (0.2 mg/kg) (not shown). Electrocardiographic leads I, II, and V_1 are simultaneously recorded with high right atrial (HRA) and His bundle electrographic (HBE) leads in this and subsequent figures. A, atrial electrogram; f, fusion beat; H, His bundle electrogram; S, stimulus.

There were 11 group IB patients with ages ranging from 18 to 60 (mean 41.7) yr (Table II). Seven patients had no apparent structural heart disease, two patients had idiopathic cardiomyopathy, and two patients had arteriosclerotic heart disease with prior myocardial infarction. All 11 patients had VT that could not be elicited by programmed atrial and programmed ventricular stimulation (Fig. 2, A and B). The onset of VT required intravenous infusion of isoproterenol at 3–8 μ g/min (Fig. 2 C) and overdrive ventricular pacing could not convert the arrhythmia to a sustained sinus rhythm. VT remained inducible and manifested the same rate during intravenous infusion of verapamil, and could resolve only by discontinuation of isoproterenol infusion. The rates of VT averaged 178.2 (140–210) beats/min. Except for one patient (case 5, Table II) with idiopathic cardiomyopathy who had VT of a right bundle branch block pattern, the remaining 10 patients manifested VT of a left bundle branch block pattern varying in frontal axes from -60° to $+130^\circ$. Treadmill exercise testing provoked the onset of VT in 5 patients (cases 2, 3, 5, 7, and 9, Table II) (Fig. 3). After β -adrenergic blockade with intravenous propranolol (0.2 mg/kg), intravenous infusion of isoproterenol (3–8 μ g/min) could no longer provoke an onset of the arrhythmia (Fig. 2 D).

Verapamil-responsive ventricular tachycardia (group II). This group consisted of 12 patients ranging in ages from 18 to 48 (mean 30.7) yr (Table III). One patient had associated idiopathic cardiomyopathy and the remaining 11 patients had no clinical evidence of structural heart disease. Characteristically, the first beat of VT started late in diastole with a premature

coupling interval of 0–90 ms shorter than the preceding QRS cycle length. The VT initiation required attaining a critical range of cycle lengths during sinus, atrial-paced, or ventricular-paced rhythm. Similar to VT in group IA patients, the arrhythmia could be terminated by overdrive ventricular pacing, but, different from VT in group IA patients, the arrhythmia could be completely suppressed by intravenous infusion of verapamil (Figs. 4 and 5).

Seven patients manifested VT of a right bundle branch block pattern and five patients of a left bundle branch block pattern, the rates of which averaged 146.3 (90–190) beats/min. In 8 of the 12 patients, VT could be initiated during both incremental atrial and incremental ventricular pacing for 15–20 beats at cycle lengths between 760 and 370 ms, but the zones of VT induction (window) varied from 20 to 320 ms. Of these eight patients, programmed ventricular extrastimulation could also initiate the onset of VT in four patients. In two patients (cases 5 and 8, Table III), the onset of VT could only be initiated by incremental atrial pacing at cycle lengths between 450 and 390 ms but not by incremental ventricular pacing. In the remaining 2 patients (cases 3 and 7, Table III), VT could be initiated by incremental ventricular pacing at cycle lengths between 320 and 260 ms but not by incremental atrial pacing. Atrial pacing at these cycle lengths in these latter two patients induced the atrioventricular nodal Wenckebach phenomenon. In 4 of the 12 patients, the interval between the initiating beat and the first beat of VT shortened progressively as the cycle length of sinus, atrial-paced, or ventricular-paced

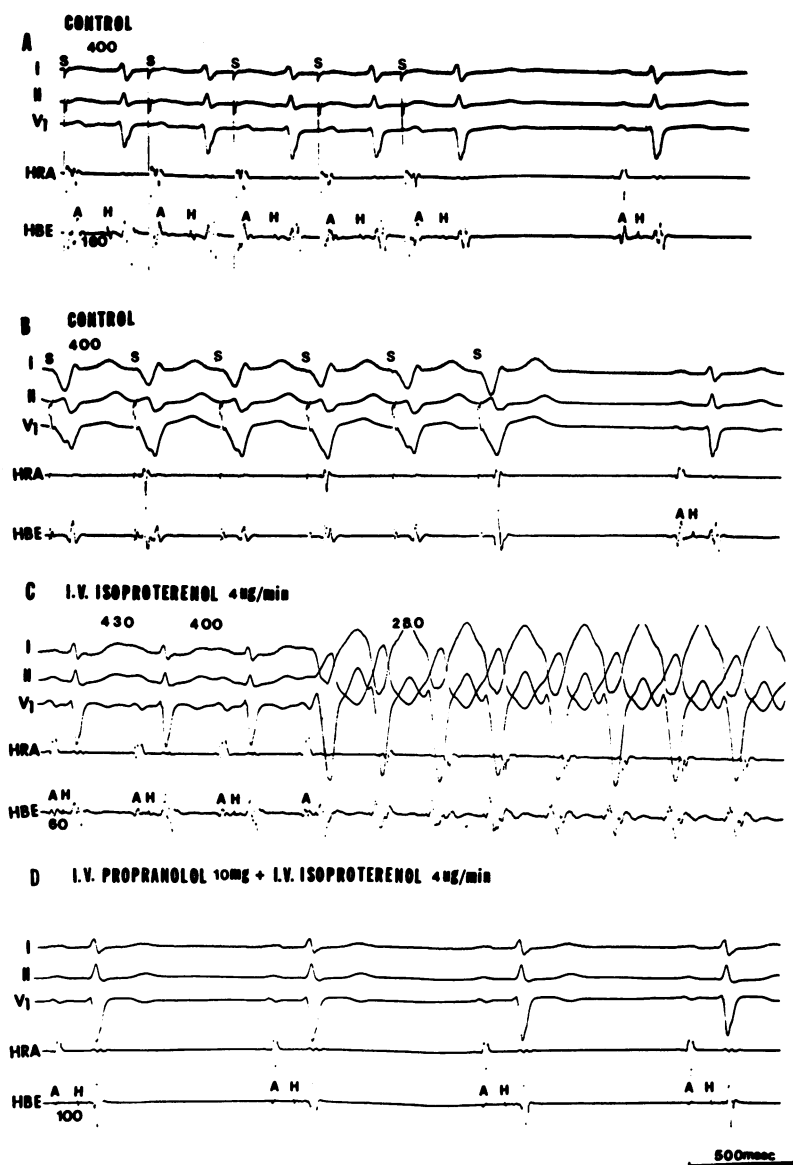


Figure 2. Provocation and suppression of VT in the verapamil-irresponsive group (IB) (case 7, Table II). VT can not be elicited by programmed atrial and programmed ventricular stimulation, but is provokable with intravenous infusion of isoproterenol. (A and B) High right atrial (HRA) and right ventricular pacing, respectively, at the cycle length (S-S) of 400 ms (comparable to that initiates VT during treadmill exercise testing as shown in Fig. 3) can not elicit the onset of VT. (C) Intravenous infusion of isoproterenol (4 µg/min) accelerates the sinus rate (cycle length shortened to 400 ms) and provokes the onset of VT with a left bundle branch block pattern (frontal axis +120°), the cycle length of which is 280 ms. (D) After β-adrenergic blockade with intravenous propranolol (0.2 mg/kg), intravenous infusion of isoproterenol (4 µg/min) can no longer provoke the onset of the arrhythmia.

beats was gradually shortened (Fig. 4). However, such a finding was not consistently observed in the remaining eight patients. Treadmill exercise testing provoked the onset of VT in 7 patients (cases 1, 2, 5, 6, 8, 9, and 10, Table III). In all 12 patients, β-adrenergic blockade with intravenous propranolol infusion (0.2 mg/kg) invariably slowed the VT rate (cycle length lengthened 40–180 ms) without suppressing its inducibility (Fig. 6). The VT became more easily inducible as the zones of VT induction were widened to 120–520 ms and shifted to the left with cycle lengths ranging from 840 to 400 ms. In six patients (cases 1, 2, 5, 7, 8, and 10, Table III) VT became continuous and could not be converted to a sustained sinus rhythm with overdrive ventricular pacing for > 1 h after β-adrenergic blockade. In each instance, intravenous infusion of 5 mg of verapamil successfully terminated the arrhythmia and established a stable sinus rhythm.

Exercise provocability and plasma catecholamine concentrations. Among the total 33 patients, treadmill exercise testing provoked the onset of VT with QRS morphologies identical to those reproduced during electrophysiology studies in 14 patients: two in group IA, five in group IB, and seven in group II

(Tables I–III). None of them experienced chest pain or developed electrocardiographic ST-T changes diagnostic of acute myocardial ischemia or infarction before the onset of VT.

The two patients in the group IA developed VT during stage I and the recovery phase, respectively. In the group IB, VT emerged during the stage III in two patients, during the stage IV in one patient, and during the recovery phase in two patients. In the group II, two patients developed VT during the stage I, three patients during the stage II, and two patients during the stage III.

The pacing cycle lengths of programmed electrical stimulation were compared with those achieved during treadmill exercise testings in these 14 patients. In the two group IA and five group IB patients, the rates of incremental atrial and incremental ventricular pacing comparable to those at which VT was provoked during treadmill exercise testing were achieved, respectively, but failed to induce the arrhythmia (Figs. 2 and 3). By contrast, in the seven group II patients, the rates of atrial-paced and/or ventricular-paced rhythm that initiated VT were comparable to those of sinus tachycardia at which VT was provoked during treadmill exercise testing (Figs. 4–8).

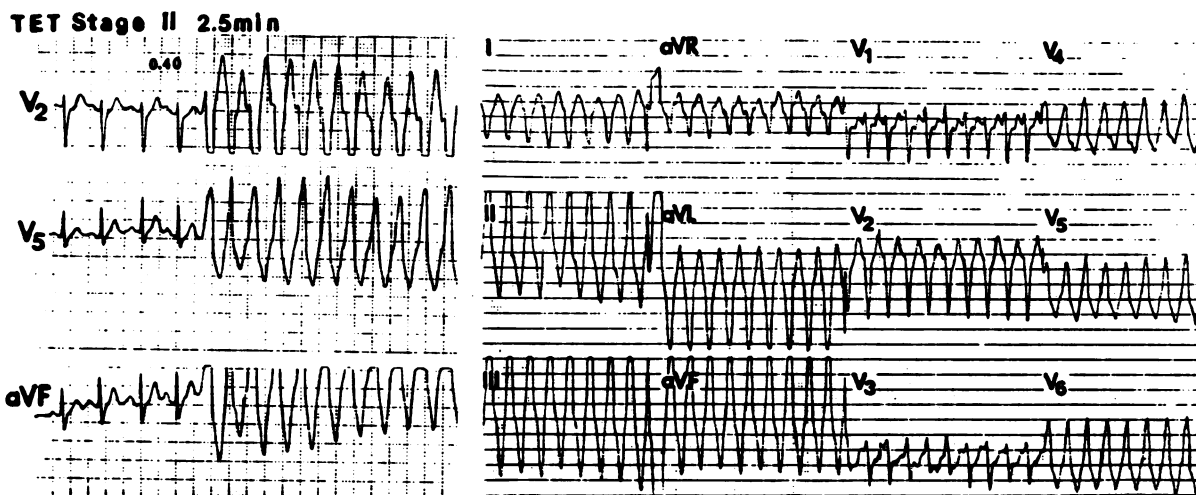


Figure 3. Provocation of VT in the verapamil-irresponsive group (IB) during treadmill exercise testing (same patient as in Fig. 2). (*Left panel*) VT emerges during the stage II of treadmill exercise testing (TET) at which time the sinus rate has accelerated to 150 beats/min (cycle length 0.40 s). Note that attainment of comparable cycle

lengths during atrial and ventricular pacing can not provoke onset of VT as shown in Fig. 2, A and B. (*Right panel*) The 12 lead electrocardiogram of the exercise-induced VT as demonstrated in the left panel. The VT has an identical QRS morphology to that provoked by isoproterenol infusion as shown in Fig. 2 C.

Hence, only in the group II patients with verapamil-responsive VT, was the initiation of VT a cycle length-dependent phenomenon.

In these 14 patients, plasma epinephrine and norepinephrine concentrations measured 38 ± 8 (20–58) pg/ml and 246 ± 65 (134–380) pg/ml, respectively, in the standing position at rest, which increased to 156 ± 28 (69–222) pg/ml and

$1,260 \pm 216$ (692–2,330) pg/ml, respectively, at stages of treadmill exercise testing during which VT was provoked. The resting values were within normal limits and those measured during treadmill exercise testing were comparable to the extent of exercise and did not appear excessive relative to what had been reported in the literature (21).

Treadmill exercise testing could not be repeated with intra-

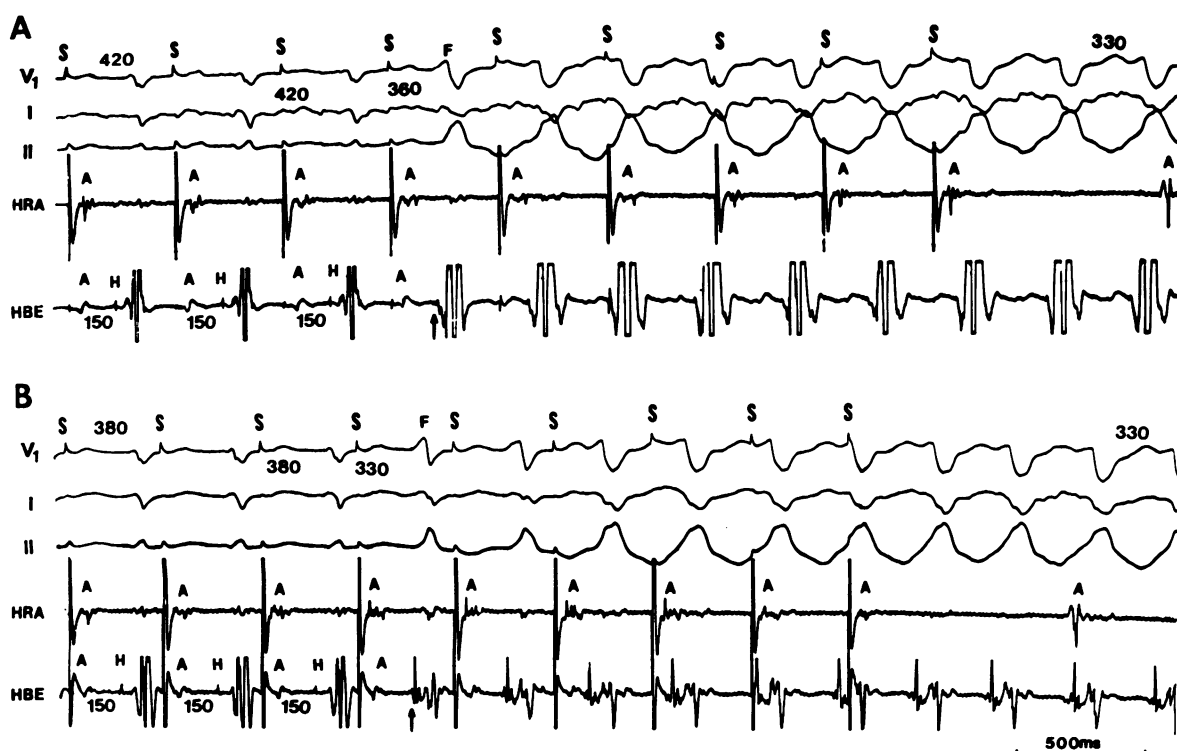


Figure 4. Induction of VT in the verapamil-responsive group (II) with programmed incremental atrial pacing (case 6, Table III). VT can be initiated by pacing either the high right atrium (HRA) or right ventricle or both while attaining a critical range of cycle lengths. (A and B) High right atrial pacing at cycle lengths between 420 and 380

ms triggers paroxysms of VT of a left bundle branch block pattern (frontal axis $+110^\circ$) with a cycle length of 330 ms. Note that the QRS interval between the last paced beat and the first beat of VT decreases when the pacing cycle length is shortened. F, fusion beat.

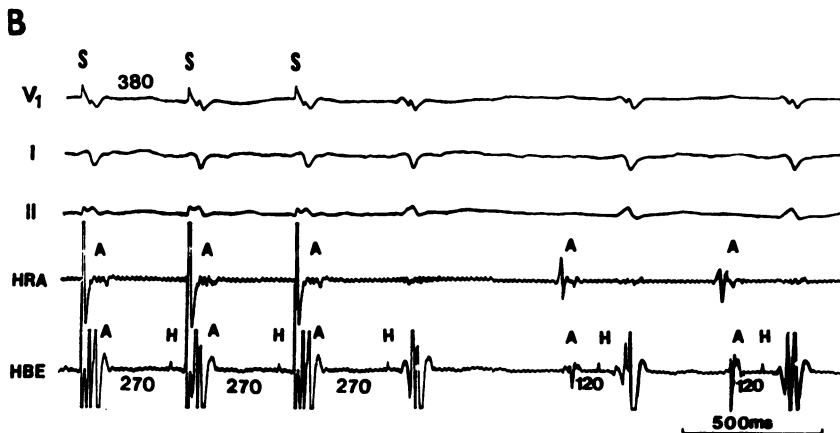
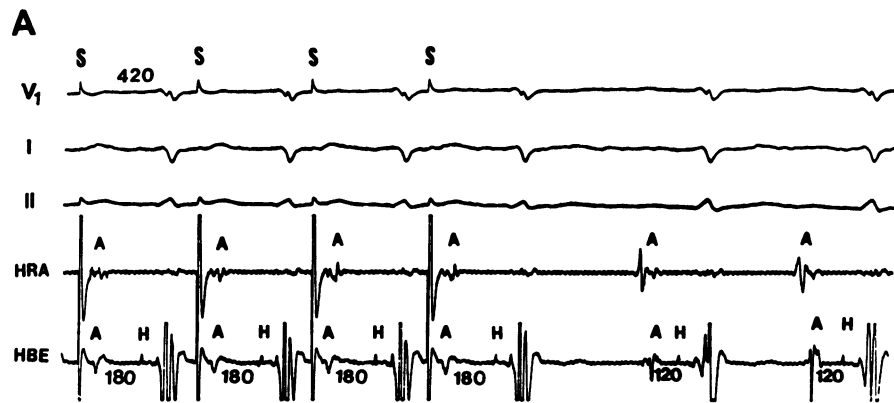


Figure 5. Suppression of VT in the verapamil-responsive group (II) with intravenous infusion of verapamil (same patient as in Fig. 4; study done on the same day). (A and B) During intravenous infusion of verapamil (0.15 mg/kg bolus followed by 0.005 mg/kg/min infusion), atrial pacing even within the previously determined critical range of cycle lengths between 420 and 380 ms can no longer trigger the onset of VT.

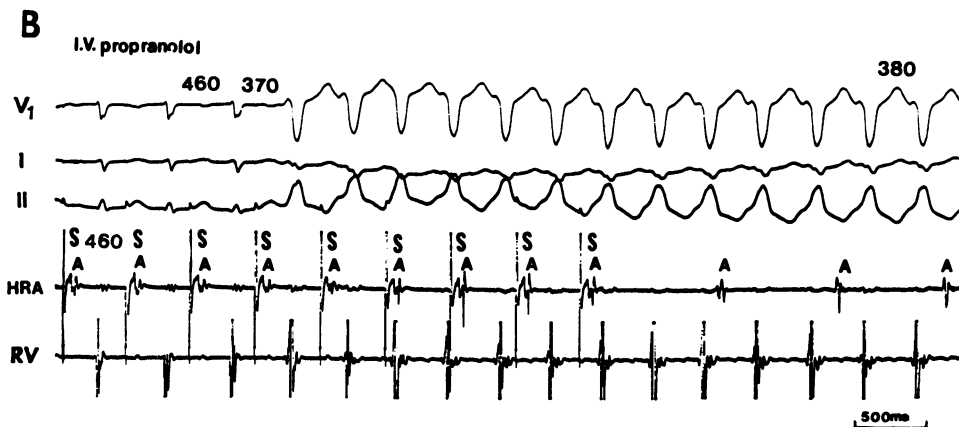
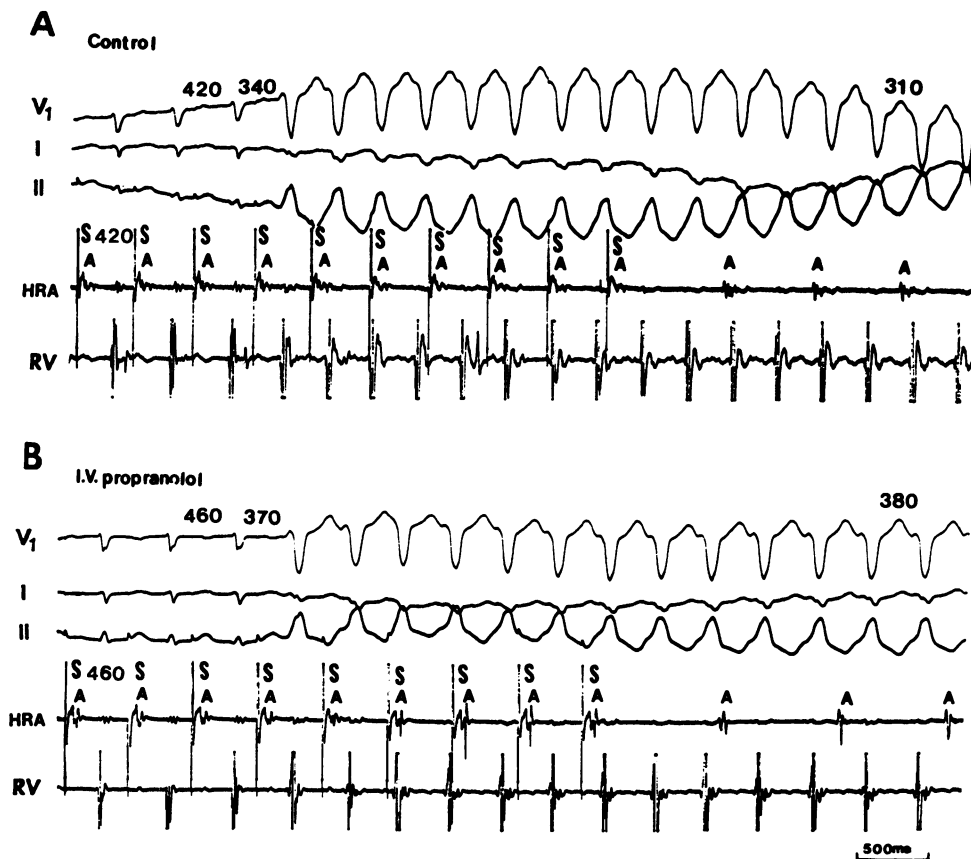


Figure 6. Effects of β -adrenergic blockade on verapamil-responsive VT (group II) (same patient as in Figs. 4 and 5; study done on a separate day) (A) At control, high right atrial pacing at a cycle length of 420 ms reproducibly initiates the onset of VT with a cycle length of 310 ms. (B) After β -adrenergic blockade with intravenous propranolol (0.2 mg/kg), the VT remains inducible during high right atrial pacing at a cycle length of 460 ms but manifests a slower rate with a cycle length of 380 ms. The critical range of cycle lengths at which VT can be initiated changes from 420–380 to 460–400 ms after β -adrenergic blockade (not shown).

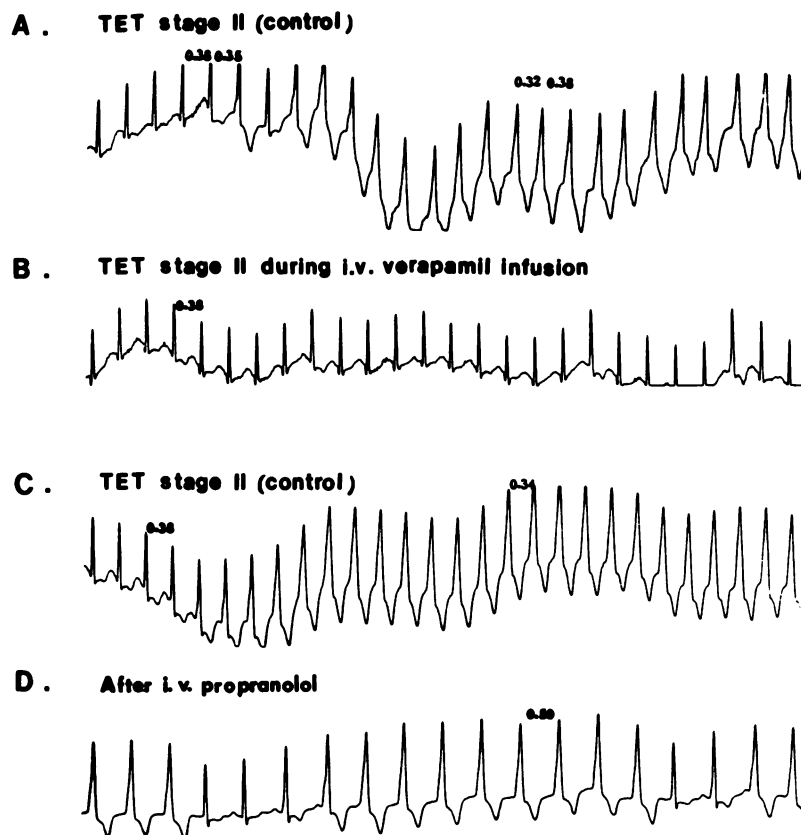


Figure 7. Verapamil-responsive VT tested with intravenous verapamil and intravenous propranolol (group II) (same patient as in Figs. 4–6). (A) At control, treadmill exercise testing (TET) accelerates the sinus rate (cycle length: 0.38 s) at the stage II and initiates an onset of VT with cycle lengths ranging from 0.32 to 0.38 s. (B) Repeated TET during verapamil infusion can no longer initiate the onset of the arrhythmia. (C) At control, VT is reproduced by TET at the stage II with sinus rate acceleration (cycle length: 0.38 s) (done on a separate day). The cycle length of VT is 0.34 s. (D) After β -adrenergic blockade, the VT slows its rate with a cycle length of 0.50 s. and becomes continuous requiring intravenous verapamil (5 mg) for termination (not shown).

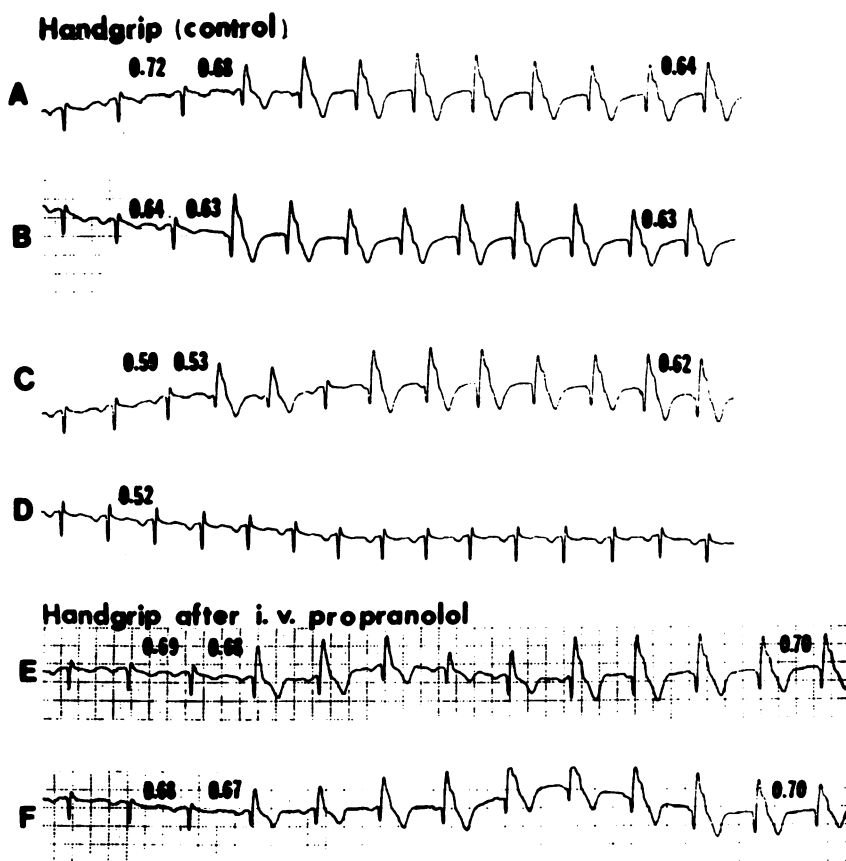


Figure 8. Effects of β -adrenergic blockade on verapamil-responsive VT (group II) (case 2, Table II). (A–C) At control, repeated handgrips accelerate the sinus rate and trigger an onset of VT. Note that the VT starts in late diastole and that there is a progressive shortening of its coupling interval (0.68–0.53 s) in response to sinus rate acceleration (cycle length 0.72–0.59 s). Also note that the QRS complex of VT is of a right bundle branch block pattern in lead V_1 . (D) Further acceleration of the sinus rate (cycle length 0.52 s) during handgrip can not initiate the onset of VT. (E and F) After β -adrenergic blockade with intravenous propranolol (0.2 mg/kg), handgrips continue to trigger the onset of VT at a slower rate (cycle length: 0.70 s).

venous propranolol in the two group IA patients because of the presence of significant heart disease and failure of intravenous propranolol to prevent VT induction during electrophysiology study. Nevertheless, intravenous propranolol prevented VT induction in the five group IB patients and slowed the VT rate in the seven group II patients during treadmill exercise testing (Figs. 7 and 8) as predicted by electrophysiology studies.

Discussion

Rationale for selection of patient population. The study was not intended to illustrate the incidence of VT of various electrophysiologic characteristics. There were two reasons why this particular cohort of 33 patients were selected for the study. First, intravenous verapamil and intravenous propranolol may, respectively, induce hypotension and/or precipitate congestive heart failure (22) at the prescribed doses. Therefore, patients with an ejection fraction of < 40% and/or a prior history of congestive heart failure were excluded. Second, VT mechanisms and responses to pharmacologic testings were considered more comparable when no severe left ventricular dysfunction was present in the whole cohort of 33 patients studied.

Effects of β -adrenergic blockade on verapamil-irresponsive ventricular tachycardia (group I). Two distinctively different responses to β -adrenergic blockade were observed between the group IA and group IB patients. In the former, VT was electrically inducible and β -adrenergic blockade was totally ineffective in suppressing the VT inducibility; in the latter, VT was not electrically inducible but was provokable with intravenous isoproterenol infusion, and β -adrenergic blockade could completely suppress the VT inducibility.

Notably all 10 group IA patients had structural heart disease with coronary arteriosclerosis with prior myocardial infarction or idiopathic cardiomyopathy (Table I). The QRS morphology of VT could be of either a right or a left bundle branch block pattern. The underlying mechanism of VT in this subset group of patients is generally believed to be due to reentry (23). Ventricular extrastimulation is usually required for induction of unidirectional block in one area and slow conduction in the other area within the reentrant circuit (24–27), and overdrive ventricular pacing, by penetrating and altering refractoriness of the reentrant circuit, may thereby terminate the arrhythmia. Because of failure of this form of VT to respond to intravenous verapamil, we have previously hypothesized that the area of slow conduction associated with infarcted human ventricular myocardium is probably composed of depressed fast sodium channels rather than calcium channel-dependent slow responses (10). This speculation is supported by the finding that, in diseased or infarcted ventricular myocardium, “poor responses” with slow conduction may be tetrodotoxin-sensitive rather than verapamil-sensitive (28, 29).

Of the 11 group IB patients with VT provokable with intravenous isoproterenol infusion, only four of them had clinical evidence of structural heart disease. The QRS morphology of VT in this subset group of patients was predominantly of a left bundle branch block pattern (Table II). Isoproterenol is a β -adrenergic agonist that enhances diastolic (phase 4) depolarization (18, 19). We have previously postulated that this form of VT is caused by catecholamine-sensitive automaticity (10).

Intravenous propranolol, by competitively antagonizing stimulation of catecholamines at β -adrenergic receptor sites, suppresses automatic VT provocability (30) with isoproterenol.

Two types of automaticity have been shown in animal Purkinje fibers: one which occurs at membrane potentials of around -90 mV referred to as “normal automaticity” and the other that occurs at membrane potentials of -40 to -60 mV referred to as “abnormal automaticity” (19, 31, 32). In response to increasing rates and duration of overdrive pacing, normal automaticity may exhibit progressive postpacing cycle length lengthening, whereas abnormal automaticity usually appears nonsuppressible and may actually slightly increase in rate. The nonsuppressibility of abnormal automaticity with overdrive pacing is attributed to the assumption that a lesser degree of sodium entry was required for impulse generation as compared with that of normal automaticity (33). Unfortunately, because of limitation of sites, rates, and duration of ventricular overdrive pacing, no attempt was made to distinguish these two types of automaticity in the present and our previous studies (10).

Effects of β -adrenergic blockade on verapamil-responsive ventricular tachycardia (group II). Patients with verapamil-responsive VT are relatively young and mostly had no clinical evidence of structural heart disease (10, 34–38). Only one of the 12 group II patients had associated idiopathic cardiomyopathy (case 11, Table III). Contrary to the claim of many investigators (34–37), verapamil-responsive VT is not confined to the QRS pattern of right bundle branch block with a superior frontal axis inasmuch as 5 of our 12 patients manifested a left bundle branch block pattern with a frontal axis varying from -75° to $+110^\circ$ (Table III).

The initiation of this form of VT depends on the attainment of a critical range of cycle lengths (10, 38). In most patients, the onset of VT can be initiated by straight atrial and straight ventricular pacing for ~ 15 –20 beats. In some patients, programmed ventricular extrastimulation can also trigger an onset of the arrhythmia. Of note, in 2 (cases 3 and 7, Table III) of our 12 patients, the VT initiation was only possible with incremental right ventricular pacing apparently because of concomitant development of atrioventricular nodal Wenckebach phenomenon during incremental right atrial pacing, which precluded attainment of the critical range of QRS cycle lengths (350–250 ms). In contrast, in the other two (cases 5 and 8, Table III) patients, the initiation of VT was possible with incremental right atrial pacing but not with programmed right ventricular stimulation. In these latter two patients, failure to initiate VT during programmed ventricular stimulation (right ventricular apex and outflow tract) was ascribed to entrance block to the arrhythmia focus. Thus, programmed atrial or programmed right ventricular stimulation alone may not expose this form of VT. Moreover, the critical range of cycle lengths for the VT initiation can be as narrow as 20 ms. Careful scanning during incremental atrial and incremental ventricular pacing is essential for exposing verapamil-responsive VT.

The mechanism of verapamil-responsive VT is uncertain and debatable: reentry versus triggered activity related to delayed afterdepolarizations (10, 34–38). Both reentry and triggered activity related to delayed afterdepolarizations are electrically inducible (23–27, 39–47). For reasons given previously (10), the interval between the initiating beat and the first beat

of VT in response to the preceding pacing cycle length or premature coupling interval should not be construed as an accurate indicator for differential diagnosis. Reentry can be responsible for verapamil-responsive VT if the genesis of VT involves calcium channel-dependent slow responses in the reentrant circuit or is caused by active myocardial ischemia reversible with calcium channel blocking agents (48, 49). Under these circumstances, β -adrenergic blockade slows the VT rate by decreasing the upstroke of slow response action potentials (50) or by counteracting a high adrenergic state which enhances myocardial conduction (51). Nevertheless, none of our group II patients had clinical evidence of acute myocardial ischemia, and despite their younger average age as compared with the group IA patients, there was no clinical evidence of a higher adrenergic tone in the group II patients. In fact, the average rate of VT was significantly slower in the group II than the group IA patients (146.3 vs. 177 beats/min, $P < 0.001$) before β -adrenergic blockade with intravenous propranolol.

Triggered activity resulting from delayed afterdepolarizations (39–47) remains a viable alternative mechanism. The initiation of triggered activity depends on previous depolarizations. Within a critical range of cycle lengths, delayed afterdepolarizations may attain threshold and elicit an action potential which, if perpetuated, can lead to a sustained rhythmic activity. The ionic currents responsible for the genesis of delayed afterdepolarizations are believed to be carried by sodium and modulated by calcium (52–54). This hypothesis is supported by the finding that delayed afterdepolarizations are suppressible with calcium channel blockers (e.g., verapamil) and with high concentrations of the fast sodium channel blocker, tetrodotoxin (43, 44). Overdrive stimulation enhances electrogenic sodium extrusion, and may thereby hyperpolarize the membrane potentials and prevent delayed afterdepolarizations from attaining threshold (55). Hence, similar to reentry, triggered activity related to delayed afterdepolarizations can not only be initiated and but also be terminated by programmed electrical stimulation.

The stimulus-evoked transmembrane calcium entry is generally believed to be via the voltage- and time-dependent channels activated by depolarization and modulated via agonist- β -adrenergic receptor interaction (56). The mechanism by which β -adrenergic stimulation increases the slow inward calcium current has been demonstrated to be mediated through the adenylate cyclase-cyclic AMP system (57–60). Stimulation of β -adrenergic receptors promotes the conversion of cytosolic ATP to cyclic AMP. Cyclic AMP activates the cyclic AMP-dependent protein kinase which phosphorylates protein constituents of the membrane-bound calcium channels. Consequently, the availability of functioning slow inward calcium channels is increased. Verapamil directly blocks the voltage- and time-dependent slow inward calcium channels (56) and may also act as a competitive β -adrenergic receptor antagonist (61). On the other hand, by competitive inhibition, propranolol circumvents the stimulatory effects of β -adrenergic agonists on the slow inward calcium current. It is tempting to postulate that verapamil-responsive VT caused by triggered activity related to delayed afterdepolarizations in our patients relies principally on the voltage- and time-dependent calcium channels with minimal dependence on agonist- β -adrenergic receptor interaction. This assumption explains why verapamil could totally suppress the VT inducibility, and why proprano-

lol could only slow the VT rate. Recently, Lerman et al. (62) described four patients with verapamil-responsive VT thought to be cyclic AMP-mediated triggered activity which was suppressible with intravenous propranolol. It may be that a diversity of biochemical and neurohormonal interactions are conducive to the genesis of verapamil-responsive VT.

Exercise-induced ventricular tachycardia. In the absence of acute myocardial ischemia or infarction, electrophysiologic mechanisms of exercise-induced VT vary among patients (8, 10). The QRS morphology of VT is not predictive of the underlying mechanism as it can be either of a right or a left bundle branch block pattern (Tables I–III). The existence of different electrophysiologic mechanisms explains why exercise-induced VT is not uniformly responsive to any specific antiarrhythmic agent (7, 8, 63, 64).

The finding that there was no excessive secretion of catecholamines at rest and during treadmill exercise testing in our 14 patients with exercise provokable VT is of interest. This inferred that the presence of a low sympathetic threshold and/or an arrhythmia-prone anatomic substrate was responsible for the occurrence of VT. Although 9 of the 14 patients had no clinically demonstrable heart disease, the possibility of their having subclinical cardiac diseases such as healed myocarditis and/or cardiomyopathy could not be excluded with certainty (65, 66).

Limitations of the study. There were practical limitations inherent to our study protocols. In using the induction of VT as the endpoint as outlined in the protocols, intravenous infusion of isoproterenol could be infused only in the group IB patients. Theoretically, isoproterenol can provoke VT of various mechanisms by exhibiting a variety of electrophysiologic effects. It enhances diastolic (phase 4) depolarization (18, 19), decreases refractory periods of myocardial tissues (51, 67), thereby allowing more degree of ventricular premature stimulation, and potentiates the development of triggered activity by accelerating the sinus rate (shortening of cycle length) and increasing intracellular cyclic AMP (18–20, 40, 41, 57–60). If the initiation of a reentrant arrhythmia or triggered rhythmic activity is solely dependent on intravenous infusion of isoproterenol, β -adrenergic blockade with intravenous propranolol may be effective in suppressing the arrhythmia inducibility. Furthermore, for near complete β -adrenergic blockade, the dose of intravenous propranolol may require up to 0.6 mg/kg of body weight (68). Such a high dose of intravenous propranolol may suppress VT of either reentry or triggered activity through inhibition of the depolarizing fast inward sodium current (69). However, such a high dose of intravenous propranolol is generally deemed clinically inappropriate.

Clinical implications. Electrophysiologic mechanisms of VT in human subjects can only be presumptive. In this study, we have attempted to bridge the gap between basic and clinical electrophysiologic principles. Reentry, catecholamine-sensitive automaticity, and triggered activity related to delayed afterdepolarizations are inferred and speculative mechanisms. Nevertheless, it can be demonstrated that, in the absence of acute myocardial ischemia or infarction, clinical and electrophysiologic characteristics of sustained VT vary among patients. Accordingly, the responses to pharmacologic agents may differ. Even in patients with recurrent sustained VT provokable with exercise, β -adrenergic blockade is not expected to be uniformly effective because of different clinical and electrophysiologic mechanisms. We recommend that clinical profiles

as well as electrophysiologic characteristics be taken into consideration while managing patients with recurrent sustained VT.

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