Effects of chronic amiodarone therapy on ventricular tachycardia induced by programmed ventricular stimulation

Several studies have reported upon the inducibility of ventricular tachycardia (VT) with programmed ventricular stimulation (PVS) during chronic amiodarone therapy; however, few studies have systematically described and compared the morphology, duration, and cycle length of VT induced by PVS before and after amiodarone. In this study, 26 patients with symptomatic VT or ventricular fibrillation were evaluated by PVS by means of one to three extrastimuli (ES) before treatment and after 2 months of amiodarone therapy. Before amiodarone, sustained unimorphic VT was induced in 21 patients (group A) and symptomatic, nonsustained VT was induced in five patients (group B). After 65 ± 8 days of amiodarone (total dose 64.5 ± 8.9 gm, mean ± S.D.), 15 of 21 patients (71%) in group A had sustained VT, five patients (24%) had nonsustained VT, and one patient had no VT induced. Four of five patients (80%) in group B had sustained VT and one patient had no VT induced. VT was induced by the same or by fewer number of ES in 79% of cases. When the morphologies of the VT induced before and after amiodarone were compared, the morphology of VT induced after amiodarone was the same in only 8 of 24 patients (33%), unimorphic but different in 14 patients (58%), and polymorphic in the remaining two patients. No correlation was found between the serum concentrations of amiodarone, desethylamiodarone, tetraiodothyronine, triiodothyronine, or reverse triiodothyroinine, and similarities or differences in VT morphology, VT cycle length, or the relative number of ES required to induce VT after treatment with amiodarone. Although VT is often still inducible after 2 months of amiodarone therapy, the VT induced is different from the baseline VT in the vast majority of patients. (Am Heart J 1987;113:57.)

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Several studies have reported upon the inducibility of ventricular tachycardia (VT) with programmed ventricular stimulation (PVS). However, there are very limited data which describe and compare the morphology, cycle length, and duration of ventricular arrhythmias initiated by PVS before and after treatment with amiodarone. Furthermore, PVS has usually been limited to two ventricular extrastimuli in almost all patients evaluated in previous studies in which detailed descriptions of the induced VT have been reported.[1-4] Because three ventricular extrastimuli may be required to induce VT in approximately 25% of patients who have a documented history of unimorphic VT, the effects of chronic administration of amiodarone upon induced VT in this subset of patients has been heretofore unknown.[5,6] The purpose of this study, therefore, was to prospectively evaluate the effects of amiodarone on VT induced by PVS in patients with a documented history of symptomatic VT or ventricular fibrillation (VF).

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METHODS

Study patients. Twenty-six patients (21 men and 5 women, age 62 ± 7 years; mean ± standard deviation) with a history of one or more episodes of symptomatic VT or VF were prospectively studied. They all met the following criteria: (1) symptomatic VT or VF did not occur in association with acute myocardial infarction, electrolyte disturbance, metabolic abnormality, or proarrythmic drug effect; (2) sustained, unimorphic VT (duration of more than 30 seconds, or requiring termination due to hemodynamic collapse) or nonsustained unimorphic VT (duration of 6 beats or ≤30 seconds) reproducing clinical symptoms could be initiated by PVS in the absence of antiarrhythmic therapy; (3) one or more conventional antiarrhythmic agents failed to control spontaneous or induced VT or were not tolerated before treatment with amiodarone; and

Table I. Clinical features of 26 patients

Patient no.	*Age/sex*	*Heart disease*	*EF*	*NYHA class*	*Arrhythmia*	*CL (msec)*	*Symptoms during VT/VF*
1	72/M	CAD	0.31	III	VF		CA
2	58/M	CAD	0.34	II	VT-S	320	Palp
3	58/M	CAD	0.20	III	VT-S	380	CHF
4	70/F	CAD	0.47	III	VT-S	320	CA
5	56/M	CAD	0.49	II	VT-S	420	Sy
6	59/M	CAD	0.59	III	VT-S	310	PSy
7	59/M	CAD		II	ND		Sy
8	67/M	CAD	0.28	III	VT-S	260	Palp
9	65/M	CAD	0.45	III	VF		CA
10	54/M	CAD	0.33	III	VT-NS	260	Palp
11	69/M	CAD	0.69	II	VF		CA
12	56/M	CAD	0.49	III	VF		CA
13	67/F	CAD	0.43	I	VT-S	220	Sy
14	57/M	CAD	0.43	III	VF		CA
15	57/F	CAD	0.37	III	VF		CA
16	70/M	CAD		III	VF		CA
17	71/M	CAD	0.12	III	VT-S	400	PSy
18	74/M	HCM	0.62	II	VT-S	320	Sy
19	64/F	CAD	0.26	IV	VF		CA
20	59/F	CAD	0.35	II	VF		CA
21	61/M	CAD	0.34	III	ND		Sy
22	54/M	CAD	0.29	II	VT-S	300	Palp
23	62/M	CAD	0.37	III	VT-S	300	PSy
24	59/M	CAD	0.23	III	VT-S	320	CA
25	64/M	CAD	0.26	III	VF		CA
26	48/M	CAD	0.48	II	VT-S	300	Sy

Abbreviations: CA = cardiac arrest; CAD = coronary artery disease; CHF = congestive heart failure; CL = cycle length; EF = ejection fraction; F = female; HCM = hypertrophic cardiomyopathy; M = male; ND = not documented; NS = nonsustained; NYHA = New York Heart Association; Palp = palpitations; PSy = presyncope; S = sustained; Sy = syncope; VF = ventricular fibrillation; VT = ventricular tachycardia.

(4) amiodarone was administered as the sole antiarrhythmic agent.

The clinical features of our study patients are summarized in Table I. Twenty-five patients had coronary artery disease, 24 of whom had a clinical history of a myocardial infarction a minimum of 6 weeks before the first spontaneous occurrence of symptomatic VT or VF. One patient had symmetric hypertrophic cardiomyopathy. The mean ejection fraction, determined in 24 of 26 patients (92%), was 0.35 ± 0.12. Before treatment with amiodarone, 12 patients had a history of cardiac arrest during which VT or ventricular fibrillation was documented. Seven patients experienced presyncope or syncope during a documented occurrence of VT; two additional patients experienced syncope after a prodrome that strongly suggested occurrence of a tachyarrhythmia. Five patients had palpitations or symptoms of congestive heart failure during documented episodes of nonsustained or sustained VT. Five patients had unimorphic VT documented by a 12-lead ECG, and 19 patients had unimorphic VT or VF documented during single-channel ECG telemetry monitoring.

After amiodarone therapy, VT was considered inducible if it had a duration of more than five beats. Sustained VT was defined as having a duration of more than 30 seconds or requiring termination due to hemodynamic collapse. Nonsustained VT was defined as having a duration of more than five beats but less than 31 seconds.

Electrophysiology study protocol. After the patients gave informed consent, they underwent an electrophysiologic study in the fasting, unsedated state, at least 4 half-lives after discontinuation of antiarrhythmic drugs. Digitalis, if required for heart failure, or beta-adrenergic blocking agents and calcium channel antagonists, if prescribed for hypertension or angina pectoris, were continued during the initial electrophysiology study, for the entire period of treatment with amiodarone, and during subsequent electropharmacologic testing of amiodarone. Two quadripolar electrode catheters were inserted percutaneously into a femoral vein and were positioned in the appropriate cardiac chamber. After the completion of atrial stimulation, whenever clinically indicated, the electrode catheters were positioned against the apex and outflow tract of the right ventricle. ECG leads V_1, I, and III, and intracardiac right ventricular electrograms were displayed on an oscilloscope and were recorded at a paper speed of 25 to 100 mm/sec with an Electronics for Medicine VR 16 recorder (Electronics for Medicine/Honeywell Inc., Pleasantville, N.Y.). Pacing was performed with a programmable stimulator (Bloom Associates,

Table II. Results of programmed ventricular stimulation in patients having ventricular tachycardia with the same morphology before and after amiodarone

	Baseline						*Amiodarone*					
Patient no.	*Morphology*	*CL (msec)*	*Site*	*DCL (msec)*	*ES*	*Method of termination*	*Morphology*	*CL (msec)*	*Site*	*DCL (msec)*	*ES*	*Method of termination*
1	IND	220	RVOT	500	3	CV(1)	IND	230	RVOT	400	3	CV(2)
2	LBB-S	260	RVA	400	3	OP(4)	LBB-S	300	RVA	400	2	OP(1)
	RBB-S	240	RVOT	400	3	OP(5)						
3	RBB-I	380	RVA	500	2	OP(7)	RBB-I	520	RVA	500	1	OP(6)
4	LBB-S	280	RVA	600	3	OP(1)	LBB-S	460	RVA	400	2	OP(1)
5	RBB-S	420	RVA	600	1	Sp	RBB-S (NS)	420	RVOT	400	3	Sp
6	RBB-I	350	RVA	400	2	OP(3)	RBB-I	600	RVOT	400	2	Sp
	LBB-S	360	RVA	400	2	OP(1)	LBB-S	400	RVA	400	3	Sp
7	RBB-S (NS)	250	RVOT	400	2	Sp	RBB-S	280	RVA	600	3	CV(1)
8	RBB-I	280	RVA	500	2	OP(1)	RBB-I	400	RVA	600	2	OP(1)
	LBB-S	280	RVA	500	2	OP(1)	IND-I	400	RVA	600	2	OP(1)

Abbreviations and symbols: CL = cycle length; CV = cardioversion; DCL = drive cycle length; ES = extrastimuli; I = inferior axis; IND = indeterminate but unimorphic; LBB = left bundle branch; No. = number; NS = nonsustained; OP = overdrive pacing; RBB = right bundle branch; RVA = right ventricular apex; RVOT = right ventricular outflow tract; S = superior axis; V = ventricular; Sp = spontaneous; numbers in parentheses = number of attempts required to successfully terminate induced ventricular tachycardia.

Narberth, Pa.). The stimuli were twice diastolic threshold and had a pulse width of 2 msec.

Our protocol for programmed ventricular stimulation has been described previously.[5] With the use of a drive train of six to eight stimuli at a cycle length of 600 or 500 msec, programmed stimulation was performed at the right ventricular apex with a single extrastimulus (S_2) until ventricular refractoriness was reached, then with double extrastimuli (S_2S_3). This was repeated with a drive cycle length of 400 msec. Due to competition during ventricular pacing, different drive cycle lengths were required in six patients. Single and double extrastimuli were then introduced at the right ventricular outflow tract by means of the same two drive cycle lengths that were used at the right ventricular apex. Programmed stimulation was then performed with the use of the same two drive cycle lengths at the right ventricular apex (RVA) with triple extrastimuli ($S_2S_3S_4$), with S_2 and S_3 initially positioned 30 msec beyond their respective points of ventricular refractoriness, and S_4 positioned 300 msec beyond S_3. Diastole was scanned with $S_2S_3S_4$ in 10 msec steps. Triple extrastimuli were then introduced at the right ventricular outflow tract (RVOT). The end point of the stimulation protocol was either one induction of VT requiring direct-current countershock for termination, or two or more inductions of sustained VT not requiring direct-current countershock.

Amiodarone therapy and follow-up electrophysiology study. Amiodarone was administered in oral doses of 1200 mg daily for 7 days, 800 mg daily for 28 days, 600 mg daily for 28 days, and then 400 mg daily thereafter. Patients were discharged from the hospital after 8 to 12 days of therapy, and were readmitted after 65 ± 8 days of treatment for electropharmacologic testing of amiodarone. Two quadripolar electrode catheters were reinserted percutaneously into a femoral vein and were repositioned against the apex and outflow tract of the right ventricle. PVS was repeated with the protocol described above.

Amiodarone was generally well tolerated by the majority of patients in this study, although several patients experienced hand tremor or mild ataxia. No patient required discontinuation of amiodarone because of adverse reaction or hospitalization for recurrent arrhythmia during the treatment period. The mean total dose at the time of the second electrophysiologic study was 46.5 ± 8.9 gm.

Quantitation of amiodarone in serum. Serum concentrations of amiodarone and its desethyl metabolite, desethylamiodarone, were determined by high-pressure liquid chromatography with the method of Flanagan et al.[7]

RESULTS

The results of PVS before and after amiodarone are summarized in Tables II and III.

Morphology and cycle length of induced VT before amiodarone. Thirty-two VTs with a uniform morphology were initiated in 26 patients before treatment with amiodarone. Unimorphic, sustained VT was initiated in 21 patients and unimorphic, nonsustained VT was initiated in five patients. Five patients had unimorphic VT with more than one morphology initiated during the baseline electrophysiologic study. The mean cycle length of VT before amiodarone was 284 ± 74 msec.

Comparison of morphology and cycle length of induced VT with spontaneous VT before amiodarone. In four of five patients whose spontaneous VT was documented with a 12-lead ECG, the VT initiated by programmed VT before amiodarone had the

Table III. Results of programmed ventricular stimulation in patients having ventricular tachycardia (VT) with a different morphology or no inducible VT after amiodarone

	Baseline						*Amiodarone*					
Patient No.	*Morphology*	*CL (msec)*	*Site*	*DCL (msec)*	*ES*	*Method of termination*	*Morphology*	*CL (msec)*	*Site*	*DCL (msec)*	*ES*	*Method of termination*
9	LBB-S	290	RVOT	400	3	OP(1)	RBB-S (NS)	320	RVA	400	3	Sp
10	RBB-S	200	RVOT	400	2	CV(1)	PM	300	RVA	600	2	CV(1)
11	LBB-S (NS)	200	RVA	450	1	Sp	PM (NS)	200	RVA	600	3	Sp
12	RBB-S	480	RVA	500	1	OP(1)	LBB-I	480	RVOT	600	2	OP(1)
13	RBB-I (NS)	205	RVA	400	3	Sp	RBB-S	250	RVA	550	2	CV(1)
14	RBB-S (NS)	240	RVOT	600	3	Sp	LBB-S	280	RVA	600	2	CV(1)
15	LBB-S	360	RVA	550	3	OP(11)	RBB-S	360	RVA	400	3	OP(1)
16	RBB-S	360	RVA	600	3	OP(1)	LBB-S (NS)	360	RVA	600	3	Sp
17	LBB-S	340	RVA	600	2	OP(1)	LBB-I	440	RVA	400	2	OP(6)-CV(1)
18	LBB-I	280	RVA	550	2	OP(33)	RBB-I (NS)	360	RVA	400	3	Sp
19	RBB-I (NS)	200	RVOT	375	3	Sp	LBB-S	290	RVOT	375	3	OP(17)-CV(1)
	RBB-S (NS)	200	RVOT	375	3	Sp						
20	LBB-S	240	RVA	600	2	OP(7)	RBB-I	320	RVA	600	2	OP(3)
21	IND	200	RVA	600	2	CV(1)	RBB-I	280	RVA	600	2	OP(10)
22	RBB-S	315	RVA	600	2	OP(5)	LBB-I	470	RVA	500	2	OP(1)
	RBB-I	280	RVA	600	2	OP(5)						
	LBB-S	200	RVA	600	2	CV(1)						
23	RBB-S	320	RVA	600	2	OP(2)	RBB-S*	280	RVA	600	2	OP(2)
							LBB-S	360	RVA	600	2	OP(1)
24	RBB-S	320	RVA	600	3	OP(3)	RBB-S*	360	RVA	600	3	Sp
							LBB-S	320	RVA	600	3	OP(1)
25	RBB-S	250	RVA	400	3	CV(1)						
26	LBB-S (NS)	240	RVA	375	2	Sp						

Abbreviations and symbols: PM = polymorphic; * = different QRS configuration and axis change of 30 to 40 degrees when compared to ventricular tachycardia induced before treatment—not due to increased duration intraventricular conduction alone. The remaining abbreviations and symbols are as in Table I.

same configuration. In the remaining patient, the induced VT before amiodarone was different when compared to spontaneous VT that had been documented by a 12-lead ECG during treatment with quinidine.

Morphology and cycle length of induced VT after amiodarone. After 65 ± 8 days of treatment with amiodarone, 28 VTs were induced in 24 of 26 patients (92%). VT was unimorphic and sustained in 18 patients (75%), unimorphic and nonsustained in four patients (17%), polymorphic and sustained in one patient (4%), and polymorphic and nonsustained in one patient (4%). In two patients VT could not be initiated by PVS after treatment with amiodarone. The mean cycle length of VT increased from 282 ± 75 msec before amiodarone to 365 ± 91 msec after amiodarone ($p < 0.01$).

Comparison of VT duration and morphology before and after amiodarone. Of the 21 patients who had sustained, unimorphic VT before treatment with amiodarone, 15 patients (71%) had sustained VT, five patients (24%) had nonsustained VT, and one patient (5%) had no VT initiated after amiodarone. Of the five patients who had nonsustained, unimorphic VT induced before amiodarone, four patients (80%) had sustained VT and one patient had no VT after amiodarone.

The morphology of VT induced after treatment with amiodarone was the same as the baseline VT in only 8 of the 24 patients (33%) in whom VT was induced after amiodarone, and different in the other 16 patients (67%). Three of the five patients who had unimorphic VT with more than one morphology initiated by PVS before amiodarone had VT with more than one morphology induced after amiodarone. Three of the remaining 21 patients (14%) who had unimorphic VT induced with only one morphology before amiodarone had unimorphic VT induced with more than one morphology initiated after amiodarone.

Comparison of cycle lengths of induced VT before and after amiodarone. In patients in whom the configuration of the induced VT remained the same before and after amiodarone, the mean cycle length increased from 311 ± 68 to 401 ± 118 msec ($p < 0.02$). In patients in whom the configuration of the induced VT differed before and after amiodarone, the mean cycle length increased from 271 ± 79 to 346 ± 74 msec ($p < 0.01$).

Comparison of ventricular effective refractory peri-

ods before and after amiodarone. The ventricular effective refractory period was compared before and after amiodarone at the same right ventricular site and at the same driven cycle length in 18 of 26 patients. The ventricular effective refractory period increased after amiodarone from 280 ± 29 to 304 ± 26 msec at a driven cycle length of 600 msec ($p < 0.02$), and from 248 ± 29 to 293 ± 32 msec at a driven cycle length of 400 msec ($p < 0.01$). No correlation was found between changes in ventricular effective refractory period and the inducibility or noninducibility of VT, the method of VT induction, changes in VT morphology, or duration of induced VT after amiodarone.

Comparison of method of induction of VT before and after amiodarone. When compared to the results of PVs before amiodarone, the same number of extrastimuli induced 17 of the 28 VTs (61%) observed after amiodarone. When the same number of extrastimuli induced VT after amiodarone, the morphology of 4 of the 17 VTs (24%) observed was the same and 13 (76%) were different. A fewer number of extrastimuli were required to induce 5 of the 28 VTs (18%) observed after amiodarone. The morphology of three of these five VTs (60%) was the same and in two (40%) it was different. A greater number of extrastimuli were required to induce 6 of the 28 VTs (21%) observed after amiodarone. The morphology of three of these six VTs (50%) was the same and in three (50%) it was different.

Comparison of site of VT induction before and after amiodarone. VT was initiated after amiodarone at the same right ventricular site in 18 of 24 patients (75%). The morphology of the VT induced after amiodarone at this site was the same as the baseline VT in six patients (33%) and different in 12 patients (67%). VT was initiated after amiodarone at a different site in 6 of 24 patients (25%). The morphology of the VT induced after amiodarone at this new site was the same as the baseline VT in three patients (50%) and different in three patients (50%).

Correlation of induction of VT with serum amiodarone, desethylamiodarone, and thyroid hormone concentrations. The following concentrations were determined in all patients from serum at the time of repeat PVS after chronic treatment with amiodarone:amiodarone ranged from 1.1 to 4.5 (mean:2.3 ± 0.7 mg/L; desethylamiodarone ranged from 0.5 to 2.2 (mean:1.3 ± 0.4) mg/L; tetraiodothyronine (T_4) ranged from 4.3 to 15.3 (mean:9.6 ± 2.7) μg/dl; triiodothyronine (T_3) ranged from 90 to 119 (mean:102 ± 7) ng/dl; reverse triiodothyronine (rT_3) ranged from 314 to 1813 (mean: 663 ± 340) ng/dl. No correlation was found between serum amiodarone, desthylamiodarone, T_4, T_3, or rT_3 concentrations and similarities or differences in VT morphology, VT cycle length, or the relative number of ventricular extrastimuli required to induce VT after treatment with amiodarone relative to the number of ventricular extrastimuli required before treatment.

Comparison of method of termination of induced VT before and after amiodarone. Before treatment with amiodarone, VT induced by PVS was terminated by a single synchronized 100 J transthoracic shock in four patients and by overdrive pacing in 14 patients. VT terminated spontaneously in six patients. After amiodarone, VT induced by PVS was terminated by a single, synchronized 100 J transthoracic shock in six patients, by two sequential 100 J transthoracic shocks in one patient, and by overdrive pacing in 11 patients. VT terminated spontaneously in six patients. Of the four patients who had induced VT terminated by cardioversion before amiodarone, two patients had induced VT terminated by cardioversion after amiodarone. One of these two patients required more than a single, synchronized 100 J transthoracic shock to terminate induced VT. The remaining two patients had induced VT terminated by overdrive pacing.

Of the 14 patients who had induced VT terminated by overdrive pacing before amiodarone, nine patients had induced VT terminated by using the same or fewer attempts with overdrive pacing after amiodarone (Tables II and III). One other patient, whose induced VT was terminated on the first attempt with overdrive pacing before amiodarone, had induced VT after amiodarone that required termination by cardioversion after six unsuccessful attempts with overdrive pacing. The remaining four patients had VT terminate spontaneously after amiodarone. Of the six patients who had induced VT terminate spontaneously before amiodarone, two patients had induced VT terminate spontaneously, three patients had induced VT that was terminated by cardioversion, and one patient had induced VT terminated by cardioversion after 17 unsuccessful attempts with overdrive pacing after amiodarone.

DISCUSSION

Antiarrhythmic effects of amiodarone. After 2 months of oral therapy with amiodarone, sustained unimorphic VT was still inducible by PVS in 84% of patients with a documented history of symptomatic VT or VT and inducible, unimorphic VT before treatment. However, in only eight patients (33%) was the configuration of the VT induced after amiodarone the same as the configuration of the

baseline VT. In the majority of patients, amiodarone suppressed the original morphology of VT induced before treatment even though VT remained inducible after treatment with the same or a fewer number of ventricular extrastimuli.

Such changes in VT morphology have not been a consistent observation during chronic amiodarone therapy in other studies. Veltri et al.[4] reported that the morphology of induced VT remained similar in each of 12 patients evaluated before and after 1.5 to 15 months of amiodarone, whereas others[1-3] have reported morphologically new VT being induced in 41% to 72% of patients after 0.75 to 18 months of amiodarone therapy. In these studies, however, PVS was usually limited to a maximum of two ventricular extrastimuli, or the protocol for inducing VT included ventricular burst pacing or introduction of ventricular stimuli during sinus rhythm or atrial pacing. Therefore, the apparent differences observed in the effect of amiodarone upon the morphology of induced VT could have been due to differences in the patient population, the programmed ventricular stimulation protocol, or the interval of time between initiation of treatment with amiodarone and evaluation of its effects in the electrophysiology laboratory.

In two patients polymorphic VT was initiated after amiodarone. The significance of this finding is not clear. Previous studies[5,6,8,9] have demonstrated this induced arrhythmia to be a nonspecific response to programmed stimulation in patients with and without documented occurrences of unimorphic VT before treatment. However, further studies may be necessary in order to address the clinical significance of polymorphic VT that is induced only after initiation of antiarrhythmic therapy.

Proarrhythmic effects of amiodarone. Several observations in this study suggested that amiodarone may have potential proarrhythmic effects. Although amiodarone suppressed by least one morphology of induced VT in three of the five patients who had more than one morphology induced before treatment, three additional patients who had only one morphology of VT induced before amiodarone had more than one morphology of VT induced after amiodarone. This observation differs from that of Reddy et al.,[3] who reported suppression of all VTs in each of four patients who had two types of VT before amiodarone and no increase in the number of morphologies induced in any other patient after amiodarone.

In 10 patients, VT with a new morphology was initiated at the same right ventricular site with the same or fewer number of ventricular extrastimuli after amiodarone. It is possible that this morphologically new VT could represent a proarrhythmic effect of amiodarone, since a similar morphology was not induced before amiodarone despite stimulation at the same ventricular site with the same number of extrastimuli and similar coupling intervals. Four of five patients (80%) who had *nonsustained* VT induced before amiodarone had *sustained* VT induced by PVS after amiodarone. This latter observation is compatible with previous studies[10-13] that have demonstrated a similar proarrhythmic effect after administration of amiodarone as well as other antiarrhythmic agents.

Correlation of results of PVS with serum amiodarone, desethylamiodarone, and thyroid hormone concentrations. No correlation was found between the serum concentrations of amiodarone or its desethyl metabolite and the results of PVS. Although it has been suggested by some investigators that amiodarone might exert its salutary effect on the myocardium because of its effects upon thyroid hormone metabolism,[14] Reddy et al.[3] observed no correlation between serum rT_3 concentrations and inducibility of VT during chronic amiodarone therapy. The results of this study extend these observations to include no correlation between serum concentrations of T_4, T_3, or rT_3 and similarities or differences in VT morphology, VT cycle length, or the relative number of ventricular extrastimuli required to initiate VT after treatment with amiodarone. It would appear unlikely, therefore, that amiodarone exerts any of its beneficial effects upon induced ventricular arrhythmias due to changes in circulating thyroid hormone concentrations.

Comparison with previous studies. The protocol for PVS in this study included a maximum of three extrastimuli in all patients studied. Three ventricular extrastimuli were required to induce 12 of 31 VTs (40%) before amiodarone and 13 of 29 VTs (45%) after amiodarone after a minimum of two extrastimuli failed to induce VT at two right ventricular sites with the use of two ventricular drive rates. This requirement of three extrastimuli to induce unimorphic VT before amiodarone is compatible with previous work,[5,15] that has demonstrated the need to use three extrastimuli to initiate VT in approximately 25% of patients with a documented history of uniform VT. In earlier studies[1-4] in which a detailed description of the induced VT has been reported, PVS has usually been limited to two ventricular extrastimuli in almost all patients. Therefore, the effects of chronic administration of amiodarone upon induced VT in this subset of patients have been heretofore unknown.

Because of the long elimination half-life of amiodarone, PVS was delayed for 2 months after the initiation of treatment with amiodarone. However, a strict comparison between the results of PVS in this study and previous studies is difficult. Previous work[16] has suggested that the maximal amiodarone effect upon ventricular effective and functional refractory periods and suppression of inducible, sustained VT occurs after 6 to 8 weeks or oral therapy. In many studies reported to date,[2, 17-22] PVS has been performed after a shorter period of amiodarone therapy, long before the elimination half-life of amiodarone and its maximal potential electrophysiologic and antiarrhythmic effects have been reached. In other studies[3, 4, 23, 24] where PVS has been performed in all patients at least 6 weeks after initiation of amiodarone therapy, the interval between the baseline and follow-up electrophysiologic studies in some reports has been as long as 15 to 18 months. After such long time intervals, the results of PVS could reflect a change in the substrate responsible for VT due to progression of underlying heart disease.

Difficulty in terminating recurrent ventricular arrhythmias during amiodarone therapy has been reported. Fogoros et al.[10] observed VT/VF become refractory to cardioversion in 5 of 77 patients (6%) treated with amiodarone. In the present study, greater difficulty was encountered in terminating induced VT during amiodarone therapy in one of two patients whose induced VT had been terminated successfully by a single synchronized transthoracic shock and in 1 of 10 patients whose induced VT had been terminated successfully by overdrive pacing before amiodarone. Four additional patients whose induced VT terminated spontaneously before amiodarone had induced VT that required termination by cardioversion after amiodarone. Two of these four patients had VT induced by the same number of ventricular extrastimuli and two patients had VT induced by a fewer number of extrastimuli after amiodarone. Therefore, the requirement of transthoracic cardioversion for these four patients cannot be explained simply on the basis of having exposed more malignant forms of VT due to more aggressive stimulation methods after administration of amiodarone.

Limitations. One limitation of this study is that documentation of clinical ventricular arrhythmias with a 12-lead ECG was possible in only a minority of patients studied. It cannot be stated with absolute certainty, therefore, that the morphology of VT induced by PVS before amiodarone treatment represented the same tachycardia that occurred clinically in all cases. Second, endocardial mapping of VT was not performed during PVS. It could not determined, therefore, whether amiodarone suppressed the original VT by suppressing the original VT focus or by changing the exit point of the original VT focus. Third, due to technical limitations, such as competition from sinus rhythm or ventricular premature depolarizations during ventricular pacing, the ventricular drive rates used during PVS before and after amiodarone was not uniform in all patients. We cannot exclude the possibility that this may have affected the number of extrastimuli required to achieve the critical coupling interval necessary for induction of VT in some patients

In conclusion, this study has demonstrated that although VT is often still inducible after 2 months of amiodarone therapy, the VT induced is different from the baseline VT in the vast majority of patients. Long-term follow-up will be necessary to assess whether this might affect the predictive accuracy of electropharmacologic testing with amiodarone.

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