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Usefulness of Electrophysiologic Study to Determine the Clinical Tolerance of Arrhythmia Recurrences During Amiodarone Therapy

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The relation of clinical and electrophysiologic variables to outcome was evaluated in 121 patients treated with amiodarone for sustained ventricular tachyarrhythmias. Electrophysiologic study was performed in all patients a mean of 14 days after beginning amiodarone therapy. Forty-six patients who were given oral amiodarone therapy experienced arrhythmia recurrence. Multivariate analysis was performed using 16 clinical and electrophysiologic variables to determine which factors were associated with 1) arrhythmia recurrence and 2) a poorly tolerated arrhythmia recurrence (that is, cardiac arrest or sudden cardiac death) during oral amiodarone therapy. No variable predicted arrhythmia recurrence. Five variables correlated significantly with a poorly tolerated arrhythmia recurrence. Hemodynamic stability of the arrhythmia induced on electrophysiologic testing during amiodarone therapy had the best predictive value ($p < 0.001$). Younger age, lower ejection fraction, a poorly tolerated rhythm at clinical presentation and absence of left ventricular aneurysm were also associated with a poorly tolerated arrhythmia recurrence.

Only 3 of 57 patients who had a well tolerated arrhythmia induced on electrophysiologic testing during amiodarone therapy had recurrence of a poorly tolerated arrhythmia versus 19 of 47 who had hemodynamically unstable arrhythmias induced during amiodarone therapy ($p < 0.001$). Thus, electrophysiologic testing during amiodarone therapy appears useful in identifying patients who are prone to have catastrophic arrhythmia recurrences and could allow for the institution of additional or alternative modes of therapy.

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Amiodarone has been widely used for the treatment of ventricular arrhythmias. We (1) and others (2) have found that most patients continue to have sustained arrhythmias inducible at electrophysiologic study during short- and long-term amiodarone therapy. It is controversial whether inducibility of arrhythmia during amiodarone therapy correlates with drug success (1–8). The selection of patients who are most suitable for amiodarone treatment is thus difficult.

We undertook this analysis in an attempt to determine whether the hemodynamic consequences of the arrhythmia induced during electrophysiologic study during amiodarone therapy or other clinical and electrophysiologic factors could identify those patients most likely to experience life-threatening symptoms with recurrence of ventricular tachycardia or fibrillation. The ability to identify patients at high risk for recurrence of an arrhythmia capable of producing life-threatening symptoms or sudden death might allow for adjunctive or alternative therapy, or both, to be instituted (9–12).

Methods

Study patients. The study group consisted of 121 patients who had 1) spontaneous sustained ventricular tachycardia or cardiac arrest; and 2) electrophysiologic studies after 10 to 21 days of amiodarone therapy. Characteristics of the group are shown in Table 1.

Definitions. Rhythms induced at electrophysiologic study and spontaneous rhythms were defined as tolerated or not tolerated by the following criteria:

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Table 1. Characteristics of the 121 Study Patients

Variable	Mean	SD	Range
Age (yr)	59	11	22 to 78
Spontaneous arrhythmia episodes (no.)	4.1	4.7	1 to 20
Failed drugs (no.)	2.7	1.8	1 to 12
Ejection fraction (%)	35	17	9 to 80
		No.	%
Sex			
Male		98	81
Female		23	19
Aneurysm (no.)		65	54
Heart disease			
Coronary artery disease		102	85
Idiopathic cardiomyopathy		14	12
Other*		5	

*Two patients had mitral valve prolapse, two had arrhythmogenic right ventricular dysplasia and one had tetralogy of Fallot.

Spontaneous rhythm. Nontolerated, hemodynamically unstable. Patients who had at least one single episode of arrhythmia that was hemodynamically unstable leading to syncope or cardiac arrest were classified as having a hemodynamically unstable arrhythmia even if other episodes of hemodynamically tolerated sustained ventricular tachycardia were present. *Tolerated.* Documented sustained ventricular tachycardia not associated with either syncope or cardiac arrest.

Induced rhythm. Nontolerated, hemodynamically unstable. Ventricular fibrillation or ventricular tachycardia associated with loss of consciousness or presyncope. *Tolerated.* Sustained ventricular tachycardia not associated with loss of consciousness or symptomatic hypotension.

Recurrent arrhythmias. Documented episodes of sustained ventricular tachycardia, cardiac arrest or syncope (without any other identifiable cause) that occurred after at least 2 weeks of oral therapy with amiodarone.

Sustained ventricular tachycardia. Ventricular tachycardia that lasted >30 seconds or was associated with hemodynamic collapse requiring cardioversion in <30 seconds.

Sudden cardiac death. Death occurring within ½ hour of the onset of symptoms or during sleep in a patient free of symptoms during the preceding 24 hours and in whom no other cause of death was discernible.

Electrophysiologic study protocol. Baseline studies were performed with patients in the fasting and nonsedated state after informed consent was obtained. Antiarrhythmic agents were discontinued 24 to 48 hours before the control study. The protocol and equipment used for programmed stimulation have been described previously in detail (13). Three or four electrode catheters were inserted percutaneously or by venous cutdown and positioned in the heart under fluoroscopic guidance. Routinely, quadripolar catheters were positioned in the high right atrium, right ventricular apex and outflow tract and a tripolar catheter was used at the atrioventricular (AV) junction for His bundle recording.

Electrical stimulation was performed with a specially designed digital stimulator and an optically isolated constant current source (Bloom Associates, Ltd.). The stimuli were rectangular pulses 1 ms in duration delivered at twice diastolic threshold. Intracardiac recordings were filtered at 30 to 500 Hz and recorded simultaneously with three electrocardiographic (ECG) leads (I, aVF and V_1).

Stimulation techniques for initiating ventricular arrhythmias during control and subsequent studies included the introduction of one to three ventricular extrastimuli during sinus rhythm or ventricular pacing at multiple cycle lengths (routinely 600 and 400 ms) from the right ventricular apex and outflow tract. Rapid ventricular pacing at cycle lengths of 400 to 250 ms was also performed for 10 to 30 seconds. End points of the electrophysiologic study were reproducible induction of sustained ventricular tachycardia, induction of ventricular fibrillation or completion of the study protocol. Patients had electrophysiologic studies performed in the control state and after 10 to 21 days (mean 14) after beginning amiodarone therapy.

Drug therapy. Amiodarone therapy was routinely instituted at a dose of 1,400 mg/day for 1 week (a total of 9.5 g). After 1 week, maintenance therapy was begun and consisted of 400 mg/day in 112 of 121 patients. Seven patients received 600 mg and two patients 800 mg daily.

Twenty-seven of our patients were treated with a type I antiarrhythmic agent during the follow-up period. In some patients this was done in an attempt to suppress arrhythmia inducibility before it became clear that most patients continue to have inducible ventricular tachycardia during amiodarone therapy despite apparent treatment success. Several other patients were part of a separate protocol to examine the effects of the addition of type 1 antiarrhythmic agents to amiodarone in patients with rapid tachycardias.

Statistical analysis. Multivariate analysis was performed using the Cox stepwise proportional hazards linear model. Variables used in the multivariate analysis are listed in Table 2. Variables such as ejection fraction and age were used as continuous variables in the multivariate analysis because dichotomizing them decreased the predictive value of the model. Because of significant covariance between arrhythmia tolerance and arrhythmia cycle length (at presentation, baseline electrophysiologic study and electrophysiologic study during amiodarone therapy) these variables were not included in statistical analysis at the same time, but sequential analysis was performed using each group of variables. Multivariate analysis was used in an attempt to identify factors associated with two outcome variables. We searched for factors associated with the presence or

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Table 2. Variables Used in Multivariate Analysis

Age
Sex
Presence of coronary artery disease
Ejection fraction
Presence of left ventricular aneurysm
Arrhythmia episodes
Failed drugs
Therapy with type I agents
Side effects
Presenting arrhythmia cycle length
Tolerance of presenting arrhythmia
Cycle length of induced arrhythmia without drug therapy
Tolerance of induced arrhythmia without drug therapy
Cycle length of induced arrhythmia during amiodarone therapy
Tolerance of induced arrhythmia during amiodarone therapy
Arrhythmia inducibility during amiodarone therapy

absence of arrhythmia recurrence during amiodarone therapy and in a separate analysis attempted to determine those factors that would identify whether or not an arrhythmia recurrence would be tolerated. We specifically wanted to identify those factors that might be associated with occurrence of cardiac death or syncope during drug therapy. In addition, because multivariate analysis requires patient information for each variable, the inducibility of a ventricular arrhythmia could not be analyzed simultaneously in an analysis that included the hemodynamic stability of rhythm induced at electrophysiologic testing. Thus, a third multivariate analysis was performed in which "tolerance" variables were not used but inducibility or noninducibility of ventricular arrhythmia was included. A probability (p) value of <0.1 was taken as significant in the Cox proportional hazards model. Life table analysis was performed using the Kaplan-Meier life table analysis technique. All values are expressed as the mean ± SD. Univariate analysis was performed using chi-square or Fisher's exact test when appropriate.

Results

Clinical presentation. Forty-nine of 121 patients had a history of hemodynamically stable ventricular tachycardia and were classified as having tolerated spontaneous arrhythmias. Seventy-two patients had a history of hemodynamically unstable presenting arrhythmias. Of these, 19 had syncope with rapid ventricular tachycardia and 53 patients had a cardiac arrest. Twenty-three of these 53 patients also had distinct episodes of hemodynamically well tolerated ventricular tachycardia. Thus 30 (25%) of the 121 patients presented with cardiac arrest alone and the remainder had at least one episode of ventricular tachycardia.

Baseline electrophysiologic study. Of the 121 patients, 110 underwent baseline electrophysiologic study while taking no antiarrhythmic agents. Ninety-eight patients (89%) had inducible sustained uniform ventricular tachycardia, 10 patients (9%) had inducible sustained polymorphic ventricular tachycardia or ventricular fibrillation and 2 did not have arrhythmias induced (one had 8 seconds of inducible nonsustained polymorphic ventricular tachycardia). Twenty (18%) had ventricular arrhythmia induced with one extrastimulus, 64 (59%) with two extrastimuli, 23 (21%) with three extrastimuli and one with rapid pacing. The mean cycle length of induced sustained uniform ventricular tachycardia was 262 ± 60 ms. At baseline electrophysiologic study, a hemodynamically unstable tachycardia was induced in 76 patients (70%) and a tolerated tachycardia was induced in 32 patients (30%).

Electrophysiologic study during amiodarone therapy. During electrophysiologic study during amiodarone therapy, 16 patients did not have arrhythmias induced (1 of them had noninducible arrhythmia at baseline), 2 had ventricular fibrillation induced and 103 patients had uniform sustained ventricular tachycardia induced. Forty-seven patients (46%) had hemodynamically stable ventricular tachycardia, and 58 patients (56%) had a hemodynamically unstable ventricular tachycardia induced. Twenty-nine patients (28%) had sustained ventricular arrhythmias induced with one extrastimulus, 54 (52%) with two extrastimuli and 22 (21%) with three extrastimuli. In 46 patients, the number of extrastimuli required to initiate the tachycardia was the same as that in the baseline study. Of the remaining patients, 36 required fewer extrastimuli than in the baseline state, 22 required more extrastimuli and 1 patient did not have a sustained ventricular tachycardia induced in the baseline state.

Eighty-nine patients had sustained ventricular tachycardia induced at both baseline and follow-up studies. In 69 of these 89 patients in whom a tachycardia of a configuration similar to that at baseline electrophysiologic study was induced, the mean cycle length of ventricular tachycardia induced at follow-up study was 314 ± 71 ms ($p < 0.05$ versus control). In 20 patients in whom ventricular tachycardia of multiple configurations and rates was induced, the tolerance of the tachycardia with the shortest cycle length induced was used for classifying patients. In the patients with a hemodynamically unstable tachycardia, the mean cycle length was 268 versus 351 ms in those patients with a tolerated tachycardia ($p < 0.001$). There was, however, some overlap between the two groups (Fig. 1).

Outcome. Seventy-four patients remain free of arrhythmia recurrence after a mean follow-up interval of 27 months (range 1 to 67) (Group 1). In 23 of these patients, amiodarone was discontinued: in 14 because of side effects, in 6 because the patients elected to undergo surgical therapy for arrhythmia rather than continue drug therapy and in 3 because patients elected to discontinue the drug on their own. In 13 of the 23 patients in whom amiodarone was discontinued, the duration of arrhythmia-free follow-up was <6 months; however, because the Cox logistic regression

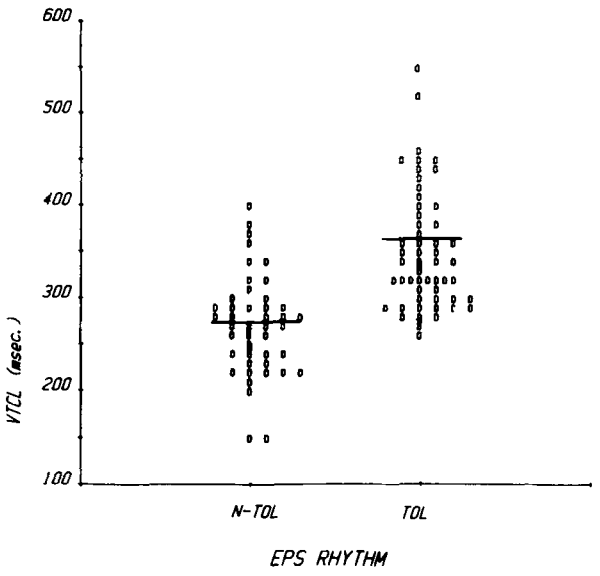

Figure 1. Relation of cycle length to clinical tolerance of ventricular tachycardia induced at electrophysiologic study during amiodarone therapy. Those patients with hemodynamically unstable tachycardia had a mean cycle length of 264 versus 350 ms in those patients with a tachycardia tolerated hemodynamically ($p < 0.05$). There was, however, significant overlap between the groups. VTCL = cycle length of ventricular tachycardia induced at electrophysiologic study; EPS RHYTHM = rhythm induced at electrophysiologic study; TOL = tolerated hemodynamically; N-TOL = hemodynamically unstable.

Table 3. Results of Multivariate Analysis: Correlation With Poorly Tolerated Recurrence

Variable	p Value
Nontolerated presenting arrhythmia	0.049
Nontolerated rhythm induced during amiodarone therapy	0.001
Absence of aneurysm	0.084
Lower ejection fraction	0.016
Younger age	0.015

analysis corrects for differences in follow-up time, these patients remained in the analysis. Forty-six patients experienced documented (41 patients) or presumed (syncope, 5 patients) arrhythmia recurrence after 2 weeks to 39 months of therapy (mean 8.6 months). All five patients who had syncope during amiodarone therapy presented initially with loss of consciousness or cardiac arrest. Twenty patients had recurrence of tolerated arrhythmia (Group 2) and 26 of nontolerated arrhythmia (Group 3). Seventeen patients died suddenly, 5 had syncope and 4 had ventricular fibrillation documented during successful resuscitation from cardiac arrest.

Of the 14 patients with side effects requiring discontinuation of amiodarone therapy, 7 had pulmonary toxicity, 2 had neurotoxicity, 2 had intolerable photosensitivity and 1 each had anorexia, psoriasis and hepatic toxicity. Twenty-three patients died of causes other than sudden cardiac death. Although 11 of these patients died of progressive and refractory congestive heart failure, it is impossible to say what role if any amiodarone played in their death because all 11 patients had a severely depressed ejection fraction before beginning drug therapy.

Variables associated with outcome during amiodarone therapy. Of note, in only 14 (13%) of the 108 patients in the study group who had inducible arrhythmia at baseline study did the arrhythmia become noninducible during amiodarone therapy. Five of these patients had arrhythmia recurrence. The inducibility of ventricular arrhythmia at electrophysiologic study did not correlate with arrhythmia recurrence or recurrence of poorly tolerated arrhythmia in either univariate or multivariate analysis. None of the variables tested were significantly correlated with arrhythmia recurrence. Multivariate analysis was then repeated to examine correlates of a poorly tolerated recurrence. In this analysis, Group 1 (those patients with no arrhythmia recurrence) and Group 2 (those with tolerated recurrence) were evaluated against Group 3 (those with nontolerated arrhythmia recurrence). Five variables had an independent predictive value for poorly tolerated arrhythmia recurrence (Table 3). The most powerful correlates were tolerance of arrhythmia induced at electrophysiologic testing during amiodarone

Figure 2. Survival curves showing the percent of patients free from sudden cardiac death in those patients with well **(dashed line)** and poorly **(solid line)** tolerated arrhythmias induced at electrophysiologic study during amiodarone therapy. Data from the 93 patients used in the multivariate analysis comparing these two groups are shown. The probability value was <0.001 for this comparison with both univariate and multivariate analysis. The number of patients remaining in each group at any given time is shown in parentheses.

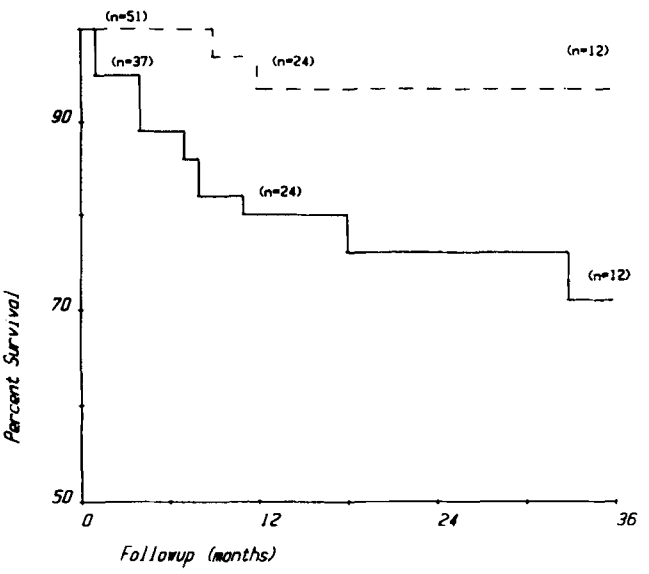

Table 4. Univariate Analysis for Those Variables Significant in the Multivariate Analysis*

Variable	Arrhythmia Recurrence		p Value
	Nontolerated†	None or Tolerated	
Base-hemodynamically unstable	21 of 26	50 of 94	$p < 0.02$
Amio-hemodynamically unstable	19 of 22	28 of 82	$p < 0.001$
Aneurysm present	13 of 25	49 of 91	NS
Ejection fraction (<35%)	17 of 25	50 of 92	NS
Age (<55 years)	8 of 26	26 of 94	NS

*No other variables were significant in univariate analysis. †Cardiac arrest or syncope as a recurrent arrhythmia. Amio-hemodynamically unstable = hemodynamically unstable arrhythmia induced at electrophysiologic study on amiodarone; Base-hemodynamically unstable = hemodynamically unstable arrhythmia induced at baseline electrophysiologic study.

therapy ($p = 0.001$), younger age ($p = 0.015$) and lower ejection fraction ($p = 0.016$). Tolerance of arrhythmia induced at electrophysiologic testing during amiodarone therapy alone provided differentiation of patients into high and low risk groups for a poorly tolerated arrhythmia recurrence through the follow-up period (Fig. 2). The r value for this variable alone was 0.245, whereas it was 0.370 for the whole model. The results of univariate analysis for those variables (with age and ejection fraction dichotomized) are shown in Table 4. The cycle length of induced ventricular tachycardia in the absence of antiarrhythmic agents was 308 ms in patients who were subsequently treated with amiodarone plus a type 1 agent versus 317 ms in those who were treated with amiodarone alone ($p = NS$). The use of a type 1 agent in this patient group was not predictive of either outcome variable.

Discussion

We studied a group of 121 patients with sustained ventricular tachyarrhythmias and found that 57% were effectively treated with amiodarone during a mean arrhythmia-free follow-up period of 27 months. Arrhythmia recurrence and sudden death rate after 1 year of amiodarone therapy were 24 and 14%, respectively. Short- and long-term success rates during amiodarone therapy in prior studies have ranged from 42 to 88% in similar patient groups (2,3,5,6). Thus, although amiodarone is useful in many patients with drug-refractory ventricular arrhythmias, treatment failures including sudden cardiac death occur in a sizable percentage of patients.

Predictors of outcome on amiodarone therapy. It is still controversial whether noninducibility or change in the mode of ventricular tachycardia induction can predict recurrence (1,6,14–17). Although we did not find a correlation between inducibility and outcome during amiodarone therapy, only 14 (13%) of 108 patients in our group who had inducible arrhythmia at baseline study became noninducible, and thus the number of patients in this group may have been too small for analysis. Unfortunately, no other clinical or electrophysiologic variable was associated with arrhythmia recurrence in our population.

This study indicates that several variables were associated with poorly tolerated arrhythmia recurrences during amiodarone therapy. These variables included the hemodynamic tolerance of the arrhythmia induced at electrophysiologic testing during amiodarone therapy which had the highest association (Fig. 2 and Table 3). Of note, 19 of the 22 patients with a poorly tolerated arrhythmia recurrence (Table 4) had a poorly tolerated arrhythmia induced in the electrophysiology laboratory during amiodarone therapy (sensitivity 86%, specificity 66%, positive predictive value 42% and negative predictive value 95%). Horowitz et al. (18) reported a similar correlation between symptoms during arrhythmias induced at electrophysiologic testing during amiodarone therapy and those at the time of recurrence.

Although often studied as a single group, patients presenting with recurrent sustained ventricular tachycardia and those presenting with cardiac arrest and ventricular fibrillation may represent separate populations with different arrhythmia substrates (19,20). We have found that patients with ventricular fibrillation have a lower incidence of inducible ventricular tachycardia or fibrillation at electrophysiologic testing than do those with recurrent ventricular tachycardia (13). Stevenson et al. (19) reported that patients with cardiac arrest were more likely to have two separate areas of myocardial infarction than were those with sustained hemodynamically tolerated ventricular tachycardia. It therefore seems likely that some patients with recurrent ventricular tachycardia constitute a group with a different natural history from that of patients with ventricular fibrillation and cardiac arrest, and it is not surprising that tolerance of their recurrent arrhythmia during amiodarone therapy might be dissimilar. It is also not surprising that the ejection fraction may determine clinical outcome with respect to arrhythmia tolerance. Patients who had a lower ejection fraction may have been less able to tolerate an arrhythmia of a given cycle length in similar situations and

thus were more likely to have poorly tolerated arrhythmia recurrences. In a patient with a given ejection fraction, the presence of an aneurysm may actually signify better residual ventricular function and thus may make a recurrent arrhythmia better tolerated. The reason that patient age helped to predict outcome cannot be easily explained. It is possible that young age may be associated with a clinical factor more likely to be associated with a poor prognosis but not assessed in this study and not used in the multivariate analysis.

Clinical implications. Our results and prior experience with amiodarone suggest that it is often, but not uniformly, effective in the therapy of sustained ventricular arrhythmias. Although a variety of factors, including the inducibility of ventricular tachycardia (18), multivariate analysis of clinical and electrophysiologic variables (21) and changes in ventricular refractoriness and cycle length of induced ventricular tachycardia at late electrophysiologic study (22) have been shown to correlate with drug success in some studies, the predictive accuracy of any of these factors has not been uniformly established by all investigators. DiCarlo et al. (21) identified a series of purely noninvasive variables that appear to predict cardiac arrest or sudden death. The major predictive variables in their analysis were history of cardiac arrest or syncope and ejection fraction of <40%, variables that we also found to have independent predictive value for recurrent syncope or arrest. Because in that study and the current one, sudden death occurred even in patients presenting with ventricular tachycardia and a high ejection fraction and because left ventricular dysfunction and cardiac arrest are common in patients considered for amiodarone therapy, there is a limit to the usefulness of these noninvasive variables.

The information from these prior studies leaves unresolved the clinical question of whether empiric therapy with a drug having <100% efficacy is appropriate in patients with a significant risk for sudden cardiac death. Our results demonstrating that only 3 (5%) of the 57 patients who had a well tolerated tachycardia induced during amiodarone therapy had sudden death or syncope over a mean 27 month follow-up period suggest an alternative approach. Electrophysiologic testing using up to three extrastimuli and rapid ventricular pacing may be employed to determine the tolerance of induced rhythm. In those patients in whom a poorly tolerated tachycardia is induced, especially if other associated variables such as low ejection fraction or a clinical history of cardiac arrest are present, additional or alternative modes of therapy such as surgery, implantable cardioverter/defibrillator or additional antiarrhythmic drug therapy might be considered.

Limitations of the current study. In evaluating the tolerance of rhythms induced at electrophysiologic study, we used an arbitrary definition of a hemodynamically stable rhythm rather than a specific cycle length of induced ventricular tachycardia because tolerance of tachycardia can vary in different patients even when cycle lengths are similar (Fig. 1). In performing multivariate analysis we found that "tolerated arrhythmias" as defined had a better correlation with outcome rhythm than did tachycardia cycle length. Nevertheless, determination of the hemodynamic stability of arrhythmia induced at electrophysiologic study may occasionally be difficult. Tachycardias with short cycle length are often rapidly terminated by burst pacing to prevent degeneration into ventricular fibrillation or other adverse consequences. In addition, 22% of our patients were treated with a type I antiarrhythmic agent during the follow-up period. Although multivariate analysis did not show that the use of type I agents was associated with outcome, the use of these agents in our study group could introduce a potential bias.

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