JACC Vol. 4, No. 3
September 1984:493–500

Comparison of Programmed Electrical Stimulation and Ambulatory Electrocardiographic (Holter) Monitoring in the Management of Ventricular Tachycardia and Ventricular Fibrillation

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Forty-four patients with primary ventricular fibrillation or recurrent ventricular tachycardia were stabilized on an antiarrhythmic drug regimen before electrophysiologic study and 24 to 72 hours of ambulatory electrocardiographic monitoring were performed. The long-term predictive value of these two tests was then compared retrospectively for a 12 to 32 month (mean 18) follow-up period, during which all patients continued receiving the same antiarrhythmic drug regimen. Electrophysiologic testing induced ventricular tachycardia (≥ 3 beats) in 26 patients; 23 had a poor clinical outcome (positive predictive value 88%), defined as sudden death or sustained ventricular tachycardia. In 18 patients with a negative electrophysiologic test, only 1 had a poor clinical outcome (negative predictive value 94%).

Ambulatory electrocardiographic monitoring accurately predicted outcome in 7 of 10 patients with a positive recording (positive predictive value 70%), defined as three or more consecutive ventricular extrasystoles, and in 17 of 34 patients with negative ambulatory monitor recordings (negative predictive value 50%). The long-term predictive accuracy of the electrophysiologic study was significantly higher than that of the ambulatory electrocardiographic monitor ($p < 0.001$). Electrophysiologic studies offer advantages over ambulatory electrocardiographic monitoring in this high risk patient group, providing a high degree of accuracy in predicting the long-term clinical response to antiarrhythmic drugs for at least 18 months.

With the development and refinement of clinical electrophysiologic techniques, especially programmed electrical stimulation, over the past decade, a new dimension has been added to the management of patients with malignant ventricular tachyarrhythmias such as ventricular tachycardia and ventricular fibrillation (1–5). Before the introduction of programmed electrical stimulation, however, the traditional approach to the management of such patients included the use of ambulatory electrocardiographic (Holter) monitoring to document the presence of ventricular arrhythmias, and attempts to ablate any demonstrated arrhythmias with one or more antiarrhythmic drugs (6,7). In this fashion, the ablation of any ventricular arrhythmia demonstrable on ambulatory monitoring has been used as an end point indicating adequate response to antiarrhythmic drug treatment. A recent report by Herling et al. (8) suggested that Holter monitoring was not predictive of antiarrhythmic drug efficacy in a group of patients with recurrent ventricular tachycardia.

Although the use of programmed electrical stimulation is becoming more widespread and has been studied in several groups of patients resuscitated from cardiac arrest (2,9,10), there remains no comparative study of the roles of Holter monitoring and electrophysiologic testing in patients who are survivors of sudden cardiac death. In this study, we retrospectively examined and compared the predictive values of these two techniques in the clinical management of patients with recurrent ventricular tachycardia or ventricular fibrillation.

Methods

Selection of patients. The study group consisted of 44 patients referred to The Johns Hopkins Hospital over a 2 year period who fulfilled the following four selection cri-

From the Cardiology Division, The Johns Hopkins Medical Institutions, Baltimore, Maryland. This work was supported in part by grants from The General Clinical Research Center (RR00035-21), Outpatient Clinical Research Center (RR00722-9), National Institutes of Health, Bethesda, Maryland, The Christian A. Johnson Endeavor Foundation, New York, New York and the American Heart Association, Maryland Affiliate, Baltimore, Maryland. Computational assistance was received from CLINFO, sponsored by National Institutes of Health Grant 5M01RR35-20. Manuscript received November 7, 1983; revised manuscript received April 16, 1984, accepted April 26, 1984.

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0735-1097/84/$3.00

teria: 1) they were successfully resuscitated at least once from ventricular fibrillation or at least twice from sustained symptomatic ventricular tachycardia, defined as causing syncope or presyncope and requiring cardioversion for termination; 2) acute myocardial infarction had not occurred in association with the cardiac arrest or for the preceding 2 weeks; 3) ventricular fibrillation or ventricular tachycardia was demonstrated during electrocardiographic monitoring before electrophysiologic study; and 4) ambulatory electrocardiographic (Holter) monitoring and electrophysiologic study were both carried out just before discharge from the hospital, with the antiarrhythmic drug regimen remaining unaltered thereafter.

Study protocol. On the basis of these four selection criteria, patients were admitted to the hospital and underwent serial drug trials with evaluation using ambulatory Holter monitoring and electrophysiologic studies. Although a patient may have undergone multiple electrocardiographic recordings and electrophysiologic studies, *only* the final electrophysiologic study and concurrent Holter monitoring records obtained before discharge or transfer were analyzed for the purposes of this study. During these final evaluation procedures, the antiarrhythmic drug regimen was unaltered and remained unaltered during the follow-up period.

The approach used in the management of these patients was carried out according to the following protocol: treatment with conventional agents was always attempted first, using quinidine, then procainamide, then disopyramide and lastly, propranolol. Even though the patient may have received one or more conventional agents before referral, these were reevaluated unless the following criteria were met: 1) an antiarrhythmic agent would not be retried if there was documented clinical toxicity or allergic reactions associated with therapeutic doses of the drug; 2) recurrent ventricular tachycardia documented electrocardiographically or recurrent syncope associated with therapeutic doses or blood levels (or both) of the antiarrhythmic agent; 3) in addition, exceptions to the use of disopyramide would be made if there was a history of New York Heart Association class III or IV congestive heart failure or of urinary retention or if the patient was an elderly man; and 4) propranolol was not used in patients with class III or IV congestive heart failure, a history of bronchospasm or insulin-requiring diabetes mellitus.

After the patients had met the requirements for conventional antiarrhythmic therapy and had provided informed consent, investigational antiarrhythmic agents were utilized, although no specific sequence was followed.

The clinical therapeutic goal was the elimination of all ventricular tachycardia from ambulatory electrocardiographic monitoring and suppression of ventricular tachycardia induced during electrophysiologic study. If ventricular tachycardia was evident on ambulatory monitoring in the hospital, the antiarrhythmic drug regimen was changed. However, if this goal could not be attained, the patient was discharged on the regimen that resulted in the greatest reduction in ventricular tachycardia defined as a salvo of three or more ventricular ectopic beats at a rate of greater than 100 beats/min on the ambulatory monitor. The latter was accepted at times, despite the induction of ventricular tachycardia during electrophysiologic study.

Electrophysiologic studies. These were carried out with electrode catheters inserted percutaneously through femoral or antecubital veins and positioned under fluoroscopic guidance at multiple intracardiac sites. Cardiac stimulation was performed with a constant current programmable impulse generator (Bloom Associates) that delivered rectangular pulses of 1 ms duration at twice the diastolic threshold (< 4 mA). Three or more catheters were used: a right atrial catheter, His electrogram recording catheter, right ventricular catheter and, when needed, a left ventricular catheter.

Modes of programmed stimulation included the V_1V_2 mode, in which a single ventricular extrastimulus is introduced after a ventricular drive of eight beats, and the $V_1V_2V_3$ mode, in which two ventricular extrastimuli are introduced after a ventricular drive of eight beats. Extrastimuli were made progressively more premature until ventricular refractoriness resulted. Finally, the V_{burst} mode was also utilized, consisting of rapid ventricular pacing for 10 beats at progressively shorter cycle lengths until ventricular refractoriness is attained. At least two right ventricular sites were tested at paced cycle lengths of 500 and 600 ms. If ventricular tachycardia was not induced, programmed stimulation was carried out at two left ventricular sites.

A positive electrophysiologic test was defined as the reproducible (that is, occurring on at least two of three attempts at the same prematurity interval) induction of three or more beats of ventricular origin occurring by intraventricular reentry, whether or not the patient was receiving drug therapy (11,12). The end point of study was the induction of sustained ventricular tachycardia, requiring either overdrive pacing or external cardioversion for termination. If nonsustained ventricular tachycardia was induced, the study was continued. For the purposes of this study, nonsustained ventricular tachycardia was defined as ventricular tachycardia of three or more beats' duration and terminating spontaneously within 30 seconds. Sustained ventricular tachycardia was defined as ventricular tachycardia persisting for more than 30 seconds or requiring termination earlier because of hemodynamic embarrassment.

Holter monitoring. Inpatient ambulatory electrocardiographic (Holter) monitoring was carried out near the time of electrophysiologic study, with the antiarrhythmic regimen being the same as that during the electrophysiologic study. Avionics model 445 two channel recorders were used with modified V_1 and V_5 leads. All recordings were scanned by an experienced technician with an Avionics Trendsetter. Permanent records were obtained for each abnormality and

were checked by one of us. A positive Holter monitor recording was defined as one showing a salvo of three or more beats of ventricular tachycardia at a rate greater than 100 beats/min.

Follow-up. After discharge, patients were followed up, either in our outpatient arrhythmia clinic or by the referring cardiologist, or both. Follow-up information was obtained from the patient and the patient's physician. A good clinical response was defined as the absence of recurrent sudden cardiac death or symptomatic sustained ventricular tachycardia, documented by surface electrocardiographic recording. A poor clinical response was defined as the presence of recurrent sudden cardiac death or symptomatic sustained ventricular tachycardia during the follow-up period. Sudden cardiac death was defined as unheralded death occurring within 1 hour of the onset of symptoms, or if the patient was found dead in bed, in the absence of any change in clinical status before going to bed.

Statistical analysis. The chi-square test and Fisher's exact test were used in determining statistical significance of the calculated predictive values. Life tables analyses were performed according to the method of Kaplan and Meier (13). The Wilcoxon method of comparing two life tables was used (14).

Results

Patient characteristics. The age range of the 37 men and 7 women was 22 to 79 years (mean 54). Thirty patients (68%) had coronary artery disease, 12 (27%) had myocardial disease, 1 (2%) had mitral valve prolapse, and 1 (2%) had no identifiable heart disease. Twenty-one patients (48%) had a history of resuscitation from at least one episode of primary ventricular fibrillation, 18 of whom had two or more episodes. Twenty-three patients (52%) had recurrent sustained ventricular tachycardia on two or more occasions, requiring medical intervention for termination. Patients with ventricular fibrillation had a history of 3.1 ± 1.7 (SD) separate episodes of ventricular fibrillation. Patients with ventricular tachycardia had a history of 2.8 ± 2.0 episodes of ventricular tachycardia.

Follow-up. The mean follow-up time for the 44 patients was 18.2 months (range 12 to 32).

Electrophysiologic study (Table 1). Of the 44 patients, 26 (59%) had a positive electrophysiologic study, defined as the reproducible induction of ventricular tachycardia of three or more beats occurring by intraventricular reentry. Thirty-four of the 44 had a control electrophysiologic study while not taking any antiarrhythmic medications, with 32 of the studies being positive. Of the 26 patients with inducible ventricular tachycardia, 14 had inducible sustained ventricular tachycardia and 12 had nonsustained ventricular tachycardia of 3 to 13 beats (mean 5.9 ± 3.2). Of the patients with a positive electrophysiologic study, 88% had a poor clinical outcome compared with only 6% of the patients with a negative study ($p < 0.001$). Eleven (92%) of the 12 patients who died suddenly during the follow-up period had a positive electrophysiologic test. Seventeen (85%) of the 20 patients with a good clinical outcome had a negative electrophysiologic study.

Table 1. Clinical Outcome as Predicted by Electrophysiologic (EP) Study

	No. of Patients	Follow-Up: Sudden Death	Follow-Up: Recurrent VT	Follow-Up: Sudden Death or VT
Positive EP study	26	11	12	23 (88%) ($p < 0.001$)
Negative EP study	18	1	0	1 (6%)

VT = ventricular tachycardia.

The only complication occurring as an apparent result of electrophysiologic study was deep venous thrombosis of the leg noted 48 hours after study in a patient with congestive heart failure and bilateral leg edema. The patient was treated with a short course of heparin and 3 months of warfarin.

Ambulatory electrocardiographic monitoring. Control Holter monitoring was carried out shortly after admission, with all patients demonstrating ventricular tachycardia, either sustained (requiring chest thump, pacing or electrical cardioversion for termination) or nonsustained (three or more consecutive beats at a rate greater than 100 beats/min, terminating spontaneously). Nine of the patients were taking antiarrhythmic drugs during the period of Holter monitoring because sustained, hemodynamically unstable ventricular tachycardia on admission precluded drug discontinuation. The remaining 35 patients had 24 to 72 hour Holter monitoring (mean duration 40 ± 19) while not taking any antiarrhythmic drugs (excluding digoxin and beta-adrenergic blocking agents for angina control). The average number of episodes of nonsustained ventricular tachycardia in these patients was 4.5 ± 6.0/24 h, and the average duration of ventricular tachycardia was 17 ± 24.5 beats. Holter monitoring was again carried out for 48 to 72 hours immediately before the electrophysiologic study, with the antiarrhythmic regimen being the same as that during the electrophysiologic study. Three patients had 24 hours of ambulatory electrocardiographic monitoring, 13 patients had 48 hours and 28 patients had 72 hours. The mean duration of Holter monitoring for the 44 patients was 61.6 ± 12 hours.

The discharge ambulatory electrocardiographic monitoring results were grouped as a function of an arrhythmia classification scheme (Table 2) (15). In the 10 patients with persistent nonsustained ventricular tachycardia on the discharge Holter record, the average number of episodes of ventricular tachycardia was 3.1 ± 1.0, and the average duration of each episode was 3.9 ± 2.5 beats. There was

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Table 2. Clinical Outcome as a Function of Arrhythmia Class on Ambulatory Electrocardiographic Monitoring

Arrhythmia Class*	No. of Patients	Follow-Up		
		Sudden Death	Recurrent VT	Sudden Death or VT
0	3	1	0	1 (33%)
1	7	3	3	6 (86%)
2	4	1	1	2 (50%)
3	8	2	2	4 (50%)
4a	12	4	0	4 (33%)
4b	10	1	6	7 (70%)

*Class 0 = no premature ventricular complexes present; class 1 = occasional premature ventricular complexes (< 30/h); class 2 = frequent premature ventricular complexes (≥ 30/h); class 3 = presence of multiform premature ventricular complexes; class 4a = presence of two consecutive ventricular extrasystoles; class 4b = presence of three or more consecutive ventricular extrasystoles. VT = ventricular tachycardia.

little correlation between arrhythmia class and ultimate clinical outcome.

Table 3 compares the presence and absence of ventricular tachycardia of three or more beats at a rate greater than 100 beats/min on ambulatory electrocardiographic monitoring. Seven (70%) of 10 patients with a positive recording had either sudden death or recurrent ventricular tachycardia on follow-up study, compared with 17 (50%) of 34 patients with a negative recording by this criterion. This does not represent a significant difference ($p = 0.26$). Eleven (92%) of the 12 patients who died suddenly during the follow-up period had a negative Holter recording, that is, the absence of three or more beats of ventricular tachycardia. Seventeen (85%) of the 20 patients with a good clinical outcome had a negative Holter recording, although premature ventricular complexes might have been present.

Antiarrhythmic drugs. The number of antiarrhythmic drugs that each patient had attempted to take and discontinued because of continued ventricular tachycardia during programmed electrical stimulation or because of patient intolerance or toxicity was 4.4 ± 2.1. The drugs were discontinued because of inefficacy in 82% and intolerance or toxicity in 18%. The antiarrhythmic drug regimens on which the 44 patients underwent electrophysiologic study and ambulatory electrocardiographic monitoring and were thereafter maintained are shown in Table 4. Beta-adrenergic blocking agents were used for the management of angina pectoris (12 patients) or hypertrophic obstructive cardiomyopathy (1 patient). Nine patients taking digitalis because of a history of congestive heart failure were maintained on this drug. Of the two patients maintained without medications, one had recurrent ventricular tachycardia and ventricular fibrillation associated with heavy alcohol intake, and no clinical recurrence of the arrhythmias after discontinuing all alcohol consumption.

The three patients with a false positive electrophysiologic study, that is, having a good clinical outcome despite a positive test, were taking one or more of the following antiarrhythmic drugs: quinidine, procainamide, a beta-adrenergic blocking agent and digoxin. Two of these patients had inducible sustained ventricular tachycardia that required external cardioversion, and the third had inducible nonsustained ventricular tachycardia of seven beats' duration. One of these three patients with a false positive test had recently

Table 3. Clinical Outcome as Predicted by Ventricular Tachycardia* on Ambulatory Electrocardiographic Monitoring

	No. of Patients	Follow-Up		
		Sudden Death	Recurrent VT	Sudden Death or VT
VT				
Present	10	1	6	7 (70%)
Absent	34	11	6	17 (50%)
p Value				= 0.26

*Ventricular tachycardia (VT) is defined here as the presence of three or more beats of ventricular tachycardia on discharge Holter monitoring.

Table 4. Antiarrhythmic Drugs Used in 44 Patients With Life-Threatening Ventricular Arrhythmias

	Good Clinical Response	Poor Clinical Response	
		Sudden Death	Recurrent VT
	(n = 20)	(n = 12)	(n = 12)
Quinidine	2	5	4
Procainamide	9	0	1
Disopyramide	3	0	1
Phenytoin	0	0	1
Aprindine	1	4	5
Tocainide	1	1	1
Flecainide	0	1	0
Amiodarone	0	1	1
Verapamil	0	0	1
Beta-adrenergic blocker	6	2	7
Digoxin	6	2	1
None	1	0	1

VT = ventricular tachycardia.

sustained an acute myocardial infarction 4½ weeks before his electrophysiologic study. No other patient had sustained a myocardial infarction in such close temporal proximity to electrophysiologic study.

Comparison of electrophysiologic study and ambulatory electrocardiographic monitoring. The positive and negative predictive values and predictive accuracy of each test are summarized in Table 5. The positive predictive value (that is, the percent of patients with a positive test who had an unfavorable outcome) shows no significant difference between the electrophysiologic study and Holter monitoring. The negative predictive value (that is, the percent of patients with a negative test who had a good clinical outcome) is significantly higher (94 versus 50%) for the electrophysiologic study ($p < 0.002$). Thus, the predictive accuracy, which reflects both the true positive and true negative results in a test population, is significantly higher for the electrophysiologic study than for ambulatory electrocardiographic monitoring, primarily because of frequent false negative tests in the latter.

Life table analysis. Figure 1 shows the Kaplan-Meier life table plots of patients undergoing electrophysiologic study and ambulatory electrocardiographic monitoring, respectively. A good clinical response, defined as the absence of sudden death or symptomatic sustained ventricular tachycardia during follow-up, is plotted as a function of the duration of follow-up after electrophysiologic study and ambulatory electrocardiographic monitoring. Figure 1A shows the significantly poorer response in patients with a positive test compared with those with a negative test ($p < 0.001$). Figure 1B shows the life table analysis plotted as a function of positive or negative ambulatory electrocardiographic recording, that is, the presence or absence of three or more beats of ventricular tachycardia on the predischarge Holter recording obtained near the time of electrophysiologic study. Although there appeared to be a trend, the difference in clinical response between the two techniques was not statistically significant ($p = 0.11$).

Table 5. Summary of the Comparative Predictive Clinical Value of Electrophysiologic (EP) Study and Ambulatory Electrocardiographic (Holter) Monitoring

	EP Study	Holter	p Value
Positive predictive value TP/(TP + FP)	88%	70%	= 0.32
Negative predictive value TN/(TN + FN)	94%	50%	< 0.002
Predictive accuracy (TP + TN)/Entire pop	91%	55%	< 0.001

Entire pop = entire test population; FN = false negative tests; FP = false positive tests; TN = true negative tests; TP = true positive tests.

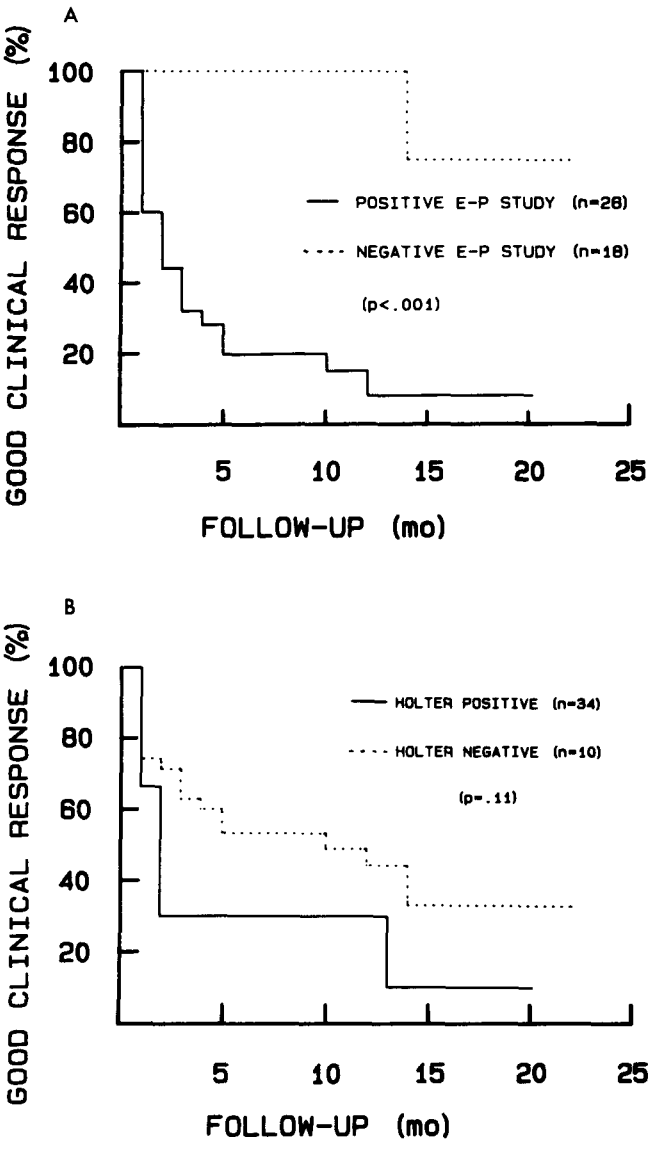

Figure 1. Kaplan-Meier life table plots of patients undergoing electrophysiologic (E-P) study (**A**) and ambulatory electrocardiographic (Holter) monitoring (**B**). Good clinical response is defined as the absence of sudden death or recurrent ventricular tachycardia in follow-up study. **A**, The response of patients with a positive electrophysiologic study is significantly poorer than that of patients with a negative study. **B**, There is no significant difference in clinical response between patients with a positive ambulatory electrocardiographic recording compared with those with a negative recording.

Discussion

Programmed electrical stimulation. Our study shows that programmed electrical stimulation has a high predictive accuracy in determining long-term antiarrhythmic drug efficacy for at least 18 months in patients with a history of primary ventricular fibrillation or recurrent ventricular tachycardia. In addition, the electrophysiologic study has a

higher predictive value than the 24 hour ambulatory electrocardiographic recording when the latter is analyzed with respect to a common arrhythmia classification scheme (15). This is consistent with the findings of Herling et al. (8), who performed 24 hour Holter monitoring in 23 patients with recurrent ventricular tachycardia, and concluded that the response of ventricular ectopic activity on Holter monitoring to antiarrhythmic or surgical therapy did not predict therapeutic success. In a recent study by Chua et al. (16), comparing programmed stimulation with ambulatory monitoring in patients similar to ours, programmed stimulation was highly predictive of long-term outcome, whereas ambulatory monitoring was found to be of limited value. The high predictive accuracy of electrophysiologic testing has been repeatedly demonstrated by numerous investigators in patients with recurrent ventricular tachycardia (3,4,17–21) and ventricular fibrillation (2,22).

Controversy and lack of uniformity remain prevalent among clinical electrophysiologists with regard both to the pacing techniques used to initiate tachyarrhythmias in the catheterization laboratory and to the number of elicited ventricular responses used to define a positive electrophysiologic test (that is, the number of induced ventricular tachycardia beats above which a given antiarrhythmic drug regimen would be considered a failure). Pacing protocols now in use include right or left (or both) ventricular single and double premature extrastimuli during ventricular pacing and brief bursts of rapid ventricular pacing (2 to 10 beats), which have been used commonly by many investigators (1–4,18–20,23,24), as well as triple premature ventricular stimuli and pacing during isoproterenol infusion, which have been used by a few groups (1,3,4). We used a pacing protocol of single and double extrastimuli during ventricular pacing and a burst of 10 ventricular paced beats from the right or left ventricle (or both), which is commonly used and whose sensitivity in this high risk patient group has been examined (23,25,26).

Although the ablation of any inducible ventricular tachycardia is sought in each patient after an antiarrhythmic drug is tested, Josephson and Horowitz (27) emphasized that only the induction of sustained ventricular tachycardia need be ablated for a drug to be considered successful. In contrast, Mason and Winkle (3) considered a drug prophylactic if five or fewer beats of ventricular tachycardia could be induced, and Ruskin et al. (2) defined arrhythmia suppression as the induction of no more than two repetitive ventricular responses after antiarrhythmic drug administration. In the present study, the induction of three or more beats of ventricular tachycardia was used to define a positive electrophysiologic test, because we have previously shown (26) that the predictive accuracy is maximized using our stimulation techniques when this criterion is used in patients with life-threatening ventricular arrhythmias.

Ambulatory electrocardiographic (Holter) monitoring. In these high risk patients, a commonly used classification system (15) of ambulatory electrocardiographic monitoring did not adequately stratify patients according to risk of recurrence of sudden death or ventricular tachycardia. We did not use the Lown grade 5 category (15), that is, the presence of the R on T wave premature ventricular complexes, because several investigators (28–32) showed that patients in this group may not be at particularly high risk of sustained ventricular tachyarrhythmias. The criterion of three or more beats of ventricular tachycardia on ambulatory electrocardiographic monitoring was used in this study to define a positive test to maximize the predictive value of the test. Follansbee et al. (31) and Bigger and Weld (32), the latter in a study of postmyocardial infarction patients, showed that the presence of ventricular tachycardia of three or more beats identifies a group of patients at highest risk of subsequent sudden death; higher than that identified by premature ventricular complex frequency, multiformity, presence of paired premature ventricular complexes or presence of R on T phenomenon.

Despite using the criterion of three or more beats of ventricular tachycardia to define a positive Holter recording, in our study the ambulatory electrocardiographic recording correctly predicted 70% of those patients who later died suddenly or had recurrent ventricular tachycardia and only 50% of those patients who had a good clinical outcome. Of those 12 patients who died during follow-up, only 1 had a positive Holter recording. This emphasizes that the primary limitation of the ambulatory electrocardiographic recording in this select, high risk patient group is likely due to the high false negative rate. Holter monitoring remains, nonetheless, a keystone in the rapid noninvasive identification of high risk subgroups (31,33–36). The presence of three or more beats of ventricular tachycardia indicates a relatively high likelihood of future sudden death or recurrent symptomatic ventricular tachycardia in both our study and those of others (31,33). This study points out the limitations of a negative ambulatory electrocardiographic monitoring and the advantage of specialized supplementary tests such as the electrophysiologic study in these high risk patients.

Limitations of the study. The predictive accuracy of a test may vary, depending on the specific patients studied, the method of testing and the specific methods used to delineate positive and negative test results. It is important to emphasize that by nature of the study design, this is a highly selected group because of the extremely high risk in these patients with recurrent ventricular tachycardia or fibrillation, and by virtue of their remaining on the fixed drug regimen during the follow-up period. We felt that it was important that patients whose antiarrhythmic drug regimen was changed after discharge, for reasons such as intolerable side effects or noncompliance, be excluded from study, because of the assumption that any change in antiarrhythmic blood levels might alter the cardiac "substrate," and that the potential for cardiac arrhythmias would change. Thus, this indepen-

dent variable, antiarrhythmic drug dosage, was kept fixed by excluding patients whose drug regimen was altered during the follow-up period.

A longer period of ambulatory electrocardiographic monitoring beyond the average of 61.6 ± 12 hours of continuous monitoring in this study might have shown different results. Indeed, several studies (37–39) have shown that because of variability of arrhythmia frequency, detection of ventricular arrhythmias is a function of the monitoring time. In general, our practice has been to obtain 3 continuous days of recordings after making a change in each patient's antiarrhythmic regimen. Only 3 of our 44 patients had no ventricular ectopic beats on their discharge Holter recording. Thus, it is possible that complete suppression of ectopic activity in this group would have resulted in a good clinical outcome (Table 2). In addition, the use of other criteria for a positive and negative test result might have improved the predictive accuracy of the Holter recording.

Although the electrophysiologic study appeared to accurately predict long-term efficacy of antiarrhythmic drugs as a group, it should not be assumed that this will be true for all drugs. Reports (40–42) have indicated, for example, that electrophysiologic studies carried out in patients taking amiodarone may not predict long-term clinical outcome. Although the mechanism is unclear, it appears that such patients may do well clinically, despite a positive electrophysiologic study. Only two of our patients were taking amiodarone; both had positive electrophysiologic studies and both had a poor clinical outcome (one died suddenly and the other had recurrent ventricular tachycardia). A related issue is that of the possible "proarrhythmic" effect of antiarrhythmic agents and the need for a control electrophysiologic study with the patient not receiving any agents whenever possible. Such a control study was not carried out in 10 of our 44 patients because of persistent, hemodynamically unstable ventricular tachycardia on admission. It should be recognized that the ability to induce ventricular tachycardia in the electrophysiology laboratory may result from the antiarrhythmic agent itself, as recently emphasized by Ruskin et al. (43). Thus, it is possible that some of these 10 patients may have had a positive electrophysiologic study or Holter monitor recording, or both, because of the drug administered, and that the antiarrhythmic therapy might be causally related to the occurrence of sudden death.

Conclusion. On the basis of this study, we conclude that in the management of patients with primary ventricular fibrillation or recurrent ventricular tachycardia, the clinician should be cognizant of the limitations of ambulatory electrocardiographic monitoring. A positive Holter recording, showing three or more beats of ventricular tachycardia, may be predictive of a poor clinical outcome in this group; yet the absence of three or more beats of ventricular tachycardia on a 48 to 72 hour record is not an accurate predictor of a good clinical outcome. The electrophysiologic study, however, has advantages over ambulatory electrocardiographic monitoring in this high risk group of patients by providing a high degree of accuracy in predicting long-term clinical response, both failures and successes, to antiarrhythmic drugs for at least 18 months.

We thank Deborah Storck, Jean Cadden and Toni Haase for secretarial assistance; technician Jennifer Beeker in the Cardiac Electrophysiology Laboratory; research technicians Sarah Ord, Marguarite Sonneborn, Charles Bauer and Sara Schmitt; and the Osler 5 research nursing staff for their excellent patient care.

References

1. Kastor JA, Horowitz LN, Harken A, Josephson ME. Clinical electrophysiology of ventricular tachycardia. N Engl J Med 1981;304:1004–19.
2. Ruskin JN, DiMarco JP, Garan H. Out of hospital cardiac arrest: electrophysiologic observations and selection of long-term antiarrhythmic therapy. N Engl J Med 1980;303:607–13.
3. Mason JW, Winkle RA. Accuracy of the ventricular tachycardia-induction study for predicting long-term efficacy and inefficacy of antiarrhythmic drugs. N Engl J Med 1980;303:1073–7.
4. Fisher JD, Cohen HL, Mehra R, Altschuler H, Escher DJW, Furman S. Cardiac pacing and pacemakers. II. Serial electrophysiologic-pharmacologic testing for control of recurrent tachyarrhythmias. Am Heart J 1977;93:658–68.
5. Wiener I. Current application of clinical electrophysiologic study in the diagnosis and treatment of cardiac arrhythmias. Am J Cardiol 1982;49:1287–92.
6. Lown B. Sudden cardiac death: the major challenge confronting contemporary cardiology. Am J Cardiol 1979;43:313–28.
7. Lown B, Podrid PJ, DeSilva RA, Graboys TB. Sudden cardiac death—management of the patient at risk. Curr Probl Cardiol 1980;5:1–62.
8. Herling IM, Horowitz LN, Josephson ME. Ventricular ectopic activity after medical and surgical treatment for recurrent sutained ventricular tachycardia. Am J Cardiol 1980;45:633–9.
9. Josephson ME, Horowitz LN, Spielman SR, Greenspan AM. Electrophysiologic and hemodynamic studies in patients resuscitated from cardiac arrest. Am J Cardiol 1980;46:948–55.
10. Myerburg RJ, Conde CA, Sung RJ. Clinical electrophysiologic and hemodynamics profile of patients resuscitated from prehospital cardiac arrest. Am J Med 1980;68:568–76.
11. Akhtar M. The clinical significance of the repetitive ventricular response (editorial). Circulation 1981;63:773–5.
12. Greene HL, Reid PR, Schaeffer AH. Mechanism of the repetitive ventricular response in man. Am J Cardiol 1980;45:227–35.
13. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. Am Stat Assoc J 1958;53:457–62.
14. Gehan EA. A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. Biometrika 1965;52:20–7.
15. Lown B, Wolf M. Approaches to sudden death from coronary heart disease. Circulation 1971;44:130–42.
16. Chua W, Roth H, Summers C, Zheutlin TA, Kehoe RF. Programmed stimulation versus ambulatory monitoring for therapy of malignant arrhythmias (abstr). Circulation 1983;68 (suppl III):III-55.
17. Hartzler GO, Maloney JD. Programmed ventricular stimulation in management of recurrent ventricular tachycardia. Mayo Clin Proc 1977;52:731–41.
18. Horowitz LN, Josephson ME, Farshidi A, Spielman S, Michelson EL, Greenspan AM. Recurrent sustained ventricular tachycardia. 3.

Role of the electrophysiologic study in selection of antiarrhythmic regimens. Circulation 1978;58:986–97.

19. Horowitz LN, Josephson ME, Kastor JA. Intracardiac electrophysiologic studies as a method for the optimization of drug therapy in chronic ventricular arrhythmia. Prog Cardiovasc Dis 1980;23:81–98.
20. Swiryn S, Wyndham C, Bauernfeind R, Dhingra R, Rosen K. Prediction of response to class I antiarrhythmic drugs during chronic electrophysiologic study of ventricular tachycardia (abstr). Circulation 1980;62 (suppl III):III-85.
21. Kehoe RF, Moran JM, Zheutlin T, Tommaso C, Lesch M. Electrophysiologic study to direct therapy in survivors of prehospital ventricular fibrillation (abstr). Am J Cardiol 1982;49:928.
22. Ruskin JN, Garan H, DiMarco JP. Electrophysiologic testing in survivors of prehospital cardiac arrest: therapy and long-term follow-up (abstr). Am J Cardiol 1982;49:958.
23. Vandepol CJ, Farshidi A, Spielman SR, Greenspan AM, Horowitz LN, Josephson ME. Incidence and clinical significance of induced ventricular tachycardia. Am J Cardiol 1980;45:725–31.
24. Wellens HJJ, Duren DR, Lie KL. Observations on mechanisms of ventricular tachycardia in man. Circulation 1976;54:237–44.
25. Platia EV, Greene HL, Vlay SC, Werner JA, Gross B, Reid PR. Sensitivity of various extrastimulus techniques in patients with serious ventricular arrhythmias. Am Heart J 1983;106:698–703.
26. Platia EV, Vlay SC, Reid PR. Predictive value of programmed electrical stimulation in patients with sudden death or recurrent ventricular tachycardia (abstr). Am J Cardiol 1981;47:397.
27. Josephson ME, Horowitz LN. Electrophysiologic approach to therapy of recurrent sustained ventricular tachycardia. Am J Cardiol 1979;43:631–42.
28. Moss AJ, DeCamilla J, Mietlowski W, Greene WA, Goldstein S, Locksley R. Prognostic grading and significance of ventricular premature beats after recovery from myocardial infarction. Circulation 1975;51/52 (suppl III):III-204–10.
29. DeSoyza N, Bissett JK, Kane JJ, Murphy ML, Doherty JE. Ectopic ventricular prematurity and its relationship to ventricular tachycardia in acute myocardial infarction in man. Circulation 1974;50:529–33.
30. Engel TR, Meister SG, Frank WS. The "R-on-T" phenomenon: an update and critical review. Ann Intern Med 1978;88:221–5.
31. Follansbee WP, Michelson EL, Morganroth J. Non-sustained ventricular tachycardia in ambulatory patients: characteristics and association with sudden cardiac death. Ann Intern Med 1980;92:741–7.
32. Bigger JT, Weld FM. Analysis of prognostic significance of ventricular arrhythmias after myocardial infarction: shortcomings of Lown grading system. Br Heart J 1981;45:717–24.
33. Bigger TJ, Weld FM, Rolnitzky LM. Prevalence, characteristics and significance of ventricular tachycardia (three or more complexes) detected with ambulatory electrocardiographic recording in the late hospital phase of acute myocardial infarction. Am J Cardiol 1981;48:815–23.
34. Kotler MN, Tabatznik B, Mower MM, Tominaga S. Prognostic significance of ventricular ectopic beats with respect to sudden death in the late post-infarction period. Circulation 1973;47:959–65.
35. Moss AJ, DeCamilla J, Engstrom F, Hoffman W, Odoroff C, David H. The post-hospital phase of myocardial infarction: identification of patients with increased mortality risk. Circulation 1974;49:460–5.
36. Vismara LA, Amsterdam EA, Mason D. Relation of ventricular arrhythmias in the late hospital phase of myocardial infarction to sudden death after hospital discharge. Am J Med 1975;59:6–12.
37. Thanararo S, Klieger RE, Hieb BR, Krone RJ, deMello VR, Oliver GC. Effect of electrocardiographic recording duration on ventricular dysrhythmia detection after myocardial infarction. Circulation 1980;62:262–5.
38. Kennedy HL, Chandra V, Sayther KL, Caralis DG. Effectiveness of increasing hours of continuous ambulatory electrocardiography in detecting maximal ventricular ectopy. Am J Cardiol 1978;42:925–30.
39. Lopes MG, Runge P, Harrison DC, Schroeder JSL. Comparison of 24 hours versus 12 hours of ambulatory ECG monitoring. Chest 1975;67:269–72.
40. Hamer AW, Finerman WB, Peter T, Mandel WJ. Disparity between the clinical and electrophysiologic effects of amiodarone in the treatment of recurrent ventricular tachyarrhythmias. Am Heart J 1981; 102:992–1000.
41. Heger J, Prystowsky EN, Jackman WM, et al. Amiodarone: clinical efficacy and electrophysiology during long-term therapy for recurrent ventricular tachycardia or ventricular fibrillation. N Engl J Med 1981;305:539–45.
42. Waxman HL, Groh WC, Marchlinski FE, et al. Amiodarone for control of sustained ventricular tachyarrhythmia: clinical and electrophysiologic effects in 51 patients. Am J Cardiol 1982;50:1066–74.
43. Ruskin JN, McGovern B, Garan H, DiMarco JP, Kelly E. Antiarrhythmic drugs: a possible cause of out-of-hospital cardiac arrest. N Engl J Med 1983;309:1302–5.