Electrophysiological Testing and Nonsustained Ventricular Tachycardia

Use and Limitations in Patients With Coronary Artery Disease and Impaired Ventricular Function

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Electrophysiological testing was performed in 100 consecutive patients with spontaneous asymptomatic nonsustained ventricular tachycardia, chronic coronary artery disease, and ejection fraction of less than 40%. Fifty-seven patients without inducible sustained ventricular arrhythmias were discharged on no antiarrhythmic therapy. Sustained monomorphic ventricular tachycardia was induced in 37 patients, and polymorphic ventricular tachycardia or ventricular fibrillation was induced in six patients. Of the 43 patients with inducible sustained ventricular arrhythmias, three had spontaneous cardiac arrest during serial drug testing and were excluded from further analysis. Twenty patients were discharged on drug therapy, resulting in suppression of inducible sustained ventricular arrhythmias. The remaining 20 patients with persistently inducible sustained arrhythmias were discharged on drug therapy, resulting in maximal rate slowing of the induced tachycardia. During a mean follow-up of 16.7 months, there were 10 recurrent cardiac arrests or sudden deaths. The 1- and 2-year actuarial incidence of these events was 2% and 6%, respectively, in patients without inducible sustained ventricular arrhythmias; 0% and 11%, respectively, in patients in whom inducible arrhythmias were suppressed; and 34% and 50%, respectively, in patients with persistently inducible sustained ventricular arrhythmias. Multivariate Cox analysis identified only the persistence of inducible sustained ventricular arrhythmias as a significant independent predictor of sudden death or recurrent sustained arrhythmias (p<0.001; relative risk, 3.5; 95% confidence intervals, 2.1–4.9). In this population, therapeutic intervention to prevent sudden death is unnecessary in patients without inducible sustained ventricular arrhythmias. However, electrophysiologically directed drug therapy as the sole treatment strategy in patients with inducible sustained ventricular arrhythmias has important limitations; only 50% of patients are drug responders, and nonresponders remain at high risk for subsequent sudden death. (Circulation 1990;82:350–358)

The treatment of asymptomatic nonsustained ventricular tachycardias in patients with coronary artery disease remains a clinical dilemma. In patients with recent myocardial infarction and impaired left ventricular function, or with chronic congestive heart failure and remote infarction, the detection of nonsustained ventricular tachycardias on ambulatory monitoring identifies a group of patients with an annual sudden death mortality of 10% or more. While prophylactic antiarrhythmic drugs or nonpharmacological therapies may benefit some of these patients, an effective strategy for selecting patients at greatest risk, predicting therapeutic efficacy, and minimizing potentially lethal proarrhythmic events has yet to be devised.

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Several recent investigations focused on the use of electrophysiological testing in stratifying risk and directing therapy in patients with nonsustained ventricular tachycardias. Study populations encompassed a broad range of ventricular function and cardiac disorders. Collectively, these studies indicate that the induction of sustained ventricular arrhythmias in patients with impaired left ventricular function, chronic coronary artery disease, and spontaneous nonsustained ventricular tachycardias may identify a subgroup at high risk of subsequent sudden death and sustained ventricular arrhythmias. Similar patients without inducible sustained arrhythmias are at much lower risk for these events.
While electrophysiological testing appears to provide a promising basis for risk stratification and assignment of therapy in this patient population, interpretation of prognostic data from previous studies is hampered by failure to stratify treatment solely and uniformly on the results of electrophysiological testing. The present study was designed to prospectively examine the use of electrophysiological testing in the prediction and prevention of sudden death in patients with documented coronary artery disease, asymptomatic nonsustained ventricular tachycardias, and impaired ventricular function. The goals of this study were to determine whether electrophysiological testing could 1) define a low-risk population without need for therapeutic intervention, 2) permit selection of effective long-term antiarrhythmic therapy in sufficient numbers of high-risk patients to justify serial electropharmacological testing, and 3) allow early identification of patients in whom drug therapy is likely to be harmful or ineffective.

Methods

Study Patients

The study group consisted of 100 consecutive patients referred to the arrhythmia service between October 1986 and December 1989 who met the criteria of 1) the presence of a nonsustained ventricular tachycardia (≥3 consecutive beats; rate, >120) on ambulatory monitoring in the absence of antiarrhythmic therapy, 2) chronic coronary artery disease without myocardial infarction or cardiac surgery within the previous 30 days, 3) left ventricular ejection fraction of less than 40%, and 4) no prior history of sustained ventricular arrhythmias, syncope, or unexplained dizziness. Nonsustained ventricular tachycardia was documented by quantitative 24-hour Holter monitoring in 81 patients and in the remainder by ambulatory telemetry monitoring. Coronary anatomy was documented by cardiac catheterization in all patients. Coronary artery disease was judged to be present if there was more than 50% reduction in luminal diameter of at least one major epicardial vessel. Assessment of left ventricular function was performed by contrast or radionuclide ventriculography in all patients.

The mean age of the population was 64±10 years. All patients had had myocardial infarction, and their mean left ventricular ejection fraction was 25±8% (range, 8–39%). Three-vessel coronary artery disease was present in 76 patients, and a history of congestive heart failure in the preceding 6 months was present in 62.

Electrophysiological Testing

Informed consent was obtained from all patients. Baseline electrophysiological testing was performed in the absence of antiarrhythmic therapy. Six surface electrocardiographic leads and intracardiac electrograms from the atrioventricular junction and the right ventricle were monitored on a multichannel oscilloscope (Siemens-Elema, Inc., Solna, Sweden), recorded on magnetic tape (model XR-510, Teac, Montebello, Calif.), and printed on an ink-jet recorder (Siemens-Elema Mingograph) at paper speeds of 100 mm/sec for subsequent review. Intracardiac electrograms were filtered at 30–500 Hz. Electrical stimulation was performed with the use of a programmable stimulator with an optically isolated constant current source (Bloom Associates, Ltd., Narberth, Pa.) delivering rectangular pulses of 2-msec duration at twice diastolic threshold.

Ventricular extrastimulus testing was performed after eight ventricular paced beats at two drive cycle lengths—600 or 500 msec (depending on intrinsic heart rate) and 400 msec. Single extrastimuli were positioned late in diastole and decremented by 10-msec intervals until refractoriness was encountered. Double extrastimuli were then introduced with the initial S2 set 20 msec beyond the refractory period and the initial S2-3 interval set at twice the S1-2 interval. The S3 was decremented in 10-msec intervals until refractoriness was encountered. The S3 was decremented by 10 msec, and then S2 again was decremented in 10-msec intervals. This process was continued until S2 encountered refractoriness. Three extrastimuli were then introduced in a similar fashion. During introduction of three extrastimuli, coupling intervals of less than 180 msec were not used. The end point of stimulation was the induction of a sustained ventricular tachyarrhythmia or completion of the entire stimulation protocol at both the right ventricular apex and right ventricular outflow tract. The induction of nonsustained ventricular tachycardia only was considered neither an end point for stimulation nor an indication for treatment. Sustained ventricular tachycardias were initiated at least twice unless the initial induced arrhythmia required DC shock for termination.

Treatment Protocol

Patients without inducible sustained ventricular arrhythmias after completion of the baseline electrophysiological study were discharged without additional testing and on no antiarrhythmic therapy (Figure 1). In patients with baseline inducible sustained ventricular arrhythmias, ventricular extrastimulus testing was repeated after intravenous loading of procainamide (15 mg/kg) or quinidine (10 mg/kg). Patients in whom inducible arrhythmias were suppressed after intravenous loading were retested after 48 hours of oral therapy.

All subsequent drug testing was performed after oral loading of antiarrhythmic drugs (at least five half-lives) and in the presence of therapeutic drug levels if applicable. Patients who did not respond to quinidine or procainamide monotherapy were tested on at least one of the following drugs or combinations—quinidine or procainamide plus mexiletine, encainide, or flecainide. The majority of patients with persistently inducible sustained arrhythmias subsequently underwent oral loading with amiodarone (1,800 mg daily for 10 days). Electrophysiological
testing was performed on amiodarone therapy after the 10-day loading period. Patients discharged on amiodarone received 800 mg daily for 2 weeks, followed by 600 mg daily for 2 weeks and then by a chronic maintenance dose of 400 mg daily.

Drug therapy was considered suppressive if it permitted less than 15 repetitive ventricular responses during completion of the entire stimulation protocol at both right ventricular sites. Patients in whom suppressive therapy was identified were discharged on that regimen. Patients in whom no suppressive therapy could be identified were discharged, when possible, on a drug regimen that produced a significantly slower (>100-msec prolongation of induced tachycardia cycle length) and hemodynamically well tolerated arrhythmia.

Follow-up

Patients were followed in the arrhythmia clinic or contacted by telephone at four monthly intervals to assess outcome, including compliance, changes in medication, and symptoms. The end points of follow-up were death, cardiac arrest with successful resuscitation, or cardiac transplantation (three patients).

Definitions

Nonsustained ventricular tachycardia. On ambulatory monitoring, nonsustained ventricular tachycardia was defined as three or more consecutive ventricular beats at a rate of more than 120 beats/min that terminated spontaneously in less than 30 seconds. For electrophysiological testing, nonsustained ventricular tachycardia was defined as lasting for five or more beats and self-terminating within 30 seconds. The tachycardia was considered monomorphic if there was a single QRS configuration and axis in each of all available surface electrocardiographic leads. All other tachycardias were considered polymorphic.

Sustained monomorphic ventricular tachycardia. Ventricular tachycardia manifesting a uniform beat-to-beat QRS configuration lasting at least 30 seconds or requiring earlier termination because of hemodynamic compromise was considered sustained.

Sustained polymorphic ventricular tachycardia or ventricular fibrillation. A ventricular tachycardia with varying beat-to-beat QRS axis and configuration lasting at least 30 seconds or requiring earlier termination because of hemodynamic compromise was considered sustained.

Sudden death. Death due to a documented ventricular tachyarrhythmia or that occurred within minutes of symptom onset or during sleep in a previously stable patient was considered sudden.

Nonsudden cardiac death. Death due to progressive circulatory failure was considered nonsudden.

Statistics

Group values are given as mean±SD or frequencies. Between-group differences were examined by paired or unpaired t tests or χ² analysis, as appropriate. Survival analysis was performed with the Kaplan-Meier method. Univariate predictors of survival were examined by the log-rank test. Multivariate predictors of survival were selected with a Cox proportional hazards model. Statistical significance was defined as a p value of less than 0.05.

Results

Spontaneous Ventricular Arrhythmias

Spontaneous nonsustained ventricular tachycardia was documented in all 100 patients. The longest run of spontaneous tachycardia in each patient ranged from three to 52 complexes—three to five complexes in 28 patients, six to 10 complexes in 40 patients, and more than 10 complexes in 32 patients. The longest run was monomorphic in 57 patients and polymorphic in the remainder. In the 81 patients with quantitative 24-hour ambulatory monitoring, the mean hourly frequency of premature ventricular complexes was 316±422 (range, 1–1,932 complexes/hr). The mean frequency of tachycardia runs during the 24-hour monitoring period in these 81 patients was 73±189 (range, 1–987 runs), including a single run in 10 patients (12%), two to five runs in 28 patients (35%), and more than five runs in 43 patients (53%).

Electrophysiological Testing

Sustained monomorphic ventricular tachycardia was initiated in 37 (37%) patients. The mean tachycardia cycle length was 249±47 msec (range, 180–400 msec). The tachycardia was initiated by one extrastimulus in one patient, two extrastimuli in seven patients, and three extrastimuli in 29 patients. Sustained polymorphic ventricular tachycardia or ventricular fibrillation was initiated in six patients, with two extrastimuli in one and three extrastimuli in five patients.
No sustained ventricular tachyarrhythmias were initiated in 57 patients. Of these patients, 18 had nonsustained ventricular tachycardias that were five to 42 complexes in duration (mean, 16±12 complexes) during completion of the stimulation protocol. All but three of the induced nonsustained tachycardias were polymorph in configuration.

Predictors of Inducible Arrhythmias

No clinical characteristics differentiated patients with from those without inducible sustained ventricular arrhythmias (Table 1). Ejection fraction was not significantly different in patients with inducible nonsustained ventricular tachycardias, sustained monomorphic ventricular tachycardias, or ventricular fibrillation than in those in whom less than five repetitive responses were initiated (Figure 2).

The characteristics of spontaneous ventricular arrhythmias prompting study entry were also examined (Table 1). Neither the frequency of premature ventricular complexes, the number of runs of ventricular tachycardia, nor the tachycardia morphology was useful in identifying patients with inducible sustained ventricular arrhythmias. Patients with inducible sustained ventricular arrhythmias had significantly longer runs of spontaneous nonsustained ventricular tachycardia (p=0.044). However, there was a broad overlap between the two patient groups (inducible, three to 52 complexes; not inducible, three to 37 complexes), diminishing the prognostic usefulness of this feature for individual patients. In addition, the morphology of the induced arrhythmia (either sustained or nonsustained) bore no relation to the morphology of spontaneous nonsustained tachycardia.

Treatment

Serial electropharmacological testing was undertaken in the 43 patients with inducible sustained arrhythmias. In three patients (7%), serious spontaneous proarrhythmic events occurred during drug testing, resulting in withdrawal from the study. All of these patients had inducible sustained monomorphic ventricular tachycardias at baseline electrophysiological testing and ejection fractions ranging from 22% to 30%. The first patient experienced a spontaneous cardiac arrest with sustained monomorphic ventricular tachycardia (cycle length, 280 msec) after the second 35-mg dose of oral encainide. The second patient had a single episode of spontaneous ventricular fibrillation (without preceding QT prolongation or torsade de pointes) after 48 hours of oral quinidine. Both patients were resuscitated without sequelae and received implantable cardioverter/defibrillators. The last patient developed typical torsades de pointes after two doses of quinidine and required multiple defibrillations. He died of circulatory failure 1 week later.

The remaining 40 patients underwent a mean of 2.3±1.1 (range, one to five) drug trials. Twenty

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Inducible (n=43)</th>
<th>Not inducible (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)*</td>
<td>63±12</td>
<td>64±8</td>
</tr>
<tr>
<td>Gender (n male) (%)</td>
<td>40 (93)</td>
<td>52 (91)</td>
</tr>
<tr>
<td>Coronary anatomy (n) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vessel</td>
<td>3 (7)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>2 vessel</td>
<td>8 (19)</td>
<td>6 (11)</td>
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<tr>
<td>3 vessel</td>
<td>32 (74)</td>
<td>44 (77)</td>
</tr>
<tr>
<td>LVEF* (%)</td>
<td>26±8</td>
<td>24±8</td>
</tr>
<tr>
<td>CHF (n) (%)</td>
<td>25 (58)</td>
<td>37 (65)</td>
</tr>
<tr>
<td>Prior CR (n) (%)</td>
<td>31 (72)</td>
<td>42 (74)</td>
</tr>
<tr>
<td>PVCS/hr (n) †</td>
<td>267±357</td>
<td>348±461</td>
</tr>
<tr>
<td>NSVT runs/24 hr (n)</td>
<td>31±59</td>
<td>99±232</td>
</tr>
<tr>
<td>Longest run NSVT (n complexes)</td>
<td>13±11</td>
<td>8±7</td>
</tr>
<tr>
<td>Monomorphic QRS morphology (%)</td>
<td>26 (60)</td>
<td>31 (54)</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; CR, coronary revascularization; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; PVCS, premature ventricular complexes.

*Mean±SD; other values are given as frequencies.
†In 81 patients.

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**Figure 2. Scatterplot of left ventricular ejection fraction stratified by baseline induced ventricular arrhythmia. Vertical bars represent mean±SD for each group. There were no significant between-group differences. Circled dots represent patients in whom inducible arrhythmias were suppressed. NI, noninducible; NSVT, nonsustained ventricular tachycardia; SMVT, sustained monomorphic ventricular tachycardia; VF, ventricular fibrillation.**
TABLE 2. Discharge Antiarrhythmic Therapy in Patients With Inducible Sustained Arrhythmias

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppressed inducible VT (n=20)</td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td>5</td>
</tr>
<tr>
<td>Encainide</td>
<td>5</td>
</tr>
<tr>
<td>Quinidine</td>
<td>2</td>
</tr>
<tr>
<td>Flecainide</td>
<td>2</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>5</td>
</tr>
<tr>
<td>Quinidine plus mexiletine</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Not suppressed inducible VT (n=20)</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>13</td>
</tr>
<tr>
<td>Amiodarone plus procainamide</td>
<td>2</td>
</tr>
<tr>
<td>Quinidine plus mexiletine</td>
<td>2</td>
</tr>
<tr>
<td>Encainide</td>
<td>3</td>
</tr>
</tbody>
</table>

VT, ventricular tachyarrhythmia.

patients (50%) were discharged on drug therapy, which resulted in complete suppression of inducible sustained ventricular arrhythmias. Ejection fractions in patients whose arrhythmias were suppressed (27±10%) did not significantly differ from those of patients whose arrhythmias were without suppression (25±8%). All six patients with induced polymorphic ventricular tachycardias or ventricular fibrillation had their arrhythmias suppressed by drug therapy. In patients with baseline induced sustained monomorphic ventricular tachycardias, the tachycardia cycle length did not significantly differ between suppressed (250±54 msec) and nonsuppressed (249±46 msec) patients.

Suppressive antiarrhythmic drug therapy was not identified in 20 patients. Five patients were not tested on amiodarone because a previously tested drug resulted in induction of slow, hemodynamically well-tolerated tachycardia (cycle length, ≥390 msec). For all 20 patients, the mean tachycardia cycle length on discharge antiarrhythmic therapy was 361±79 msec and was significantly longer than the baseline tachycardia cycle length (249±46 msec; p<0.01). In 14 of 20 patients, the tachycardia cycle length was prolonged by more than 100 msec. Antiarrhythmic therapy at the time of discharge is summarized in Table 2.

No attempt was made to standardize additional therapy. β-Blocker therapy was used in six of 57 patients (11%) without inducible ventricular arrhythmias, two of 20 patients (10%) in whom inducible ventricular arrhythmias were suppressed, and one of 20 patients (5%) with persistently inducible ventricular arrhythmias. Similarly, angiotensin converting enzyme inhibitors were administered in 33 of 57 patients (58%), 13 of 20 patients (65%), and 12 of 20 patients (60%), respectively.

Follow-up

The 97 patients without in-hospital cardiac arrest during serial drug testing were followed for a mean of 16.7 months (range, 1–39 months). Eight patients died suddenly, and two patients experienced nonfatal cardiac arrest. The overall actuarial incidence of cardiac arrest or sudden death at 1 and 2 years was 9% and 17%, respectively.

The incidence of cardiac arrest or sudden death stratified by discharge treatment group is given in Figure 3. Sudden death occurred in only two of 57 patients without baseline sustained ventricular arrhythmias, resulting in a 1- and 2-year incidence of 2% and 6%, respectively. Of the 20 patients in whom inducible sustained ventricular arrhythmias were suppressed, one patient (receiving quinidine plus mexiletine therapy) died suddenly at 15 months, resulting in a 1- and 2-year actuarial incidence of 0% and 11%, respectively. The difference between these two groups of patients was not significant. In contrast, there was a significantly greater incidence of recurrent cardiac arrest or sudden death in the 20

![Figure 3. Actuarial incidence of sudden death or cardiac arrest in 97 patients, stratified by treatment subgroup. Three patients with cardiac arrest during serial drug testing are not included in this analysis. SD, sudden death; CA, cardiac arrest.](image-url)
patients with persistently inducible sustained ventricular arrhythmias on discharge antiarrhythmic therapy ($p<0.001$). Seven patients had recurrent cardiac arrest or sudden death during follow-up (amiodarone, six patients; encainide, one patient), resulting in a 1- and 2-year actuarial incidence of 34% and 50%, respectively.

Predictors of sudden death or cardiac arrest were examined among 12 clinical and treatment variables, including age, sex, ejection fraction, prior coronary revascularization, coronary anatomy, history of congestive heart failure, presence of baseline inducible sustained ventricular arrhythmia, persistence of inducible sustained ventricular arrhythmia on therapy, duration of longest run of spontaneous ventricular tachycardia, morphology of spontaneous ventricular tachycardia, $\beta$-blocker therapy, and angiotensin converting enzyme inhibitor therapy. Both the presence of baseline inducible sustained ventricular arrhythmias ($p=0.007$) and the persistence of inducible sustained ventricular arrhythmias on therapy ($p<0.001$) were significant univariate predictors. In addition, greater length of spontaneous runs of nonsustained ventricular tachycardia also predicted sudden death or cardiac arrest by univariate analysis ($p=0.046$). However, only the persistence of inducible, sustained ventricular arrhythmias on discharge antiarrhythmic therapy was a significant independent predictor of cardiac arrest or sudden death in the multivariate Cox analysis ($p<0.001$; relative risk, 3.5; 95% confidence intervals, 2.1–4.9).

The influence of baseline inducible ventricular tachycardia characteristics on the subsequent occurrence of cardiac arrest or sudden death was also examined. Of 34 patients with baseline sustained monomorphic ventricular tachycardias (excluding three who were withdrawn due to in-hospital drug-related cardiac arrest), seven (21%) had sudden death or cardiac arrest during long-term follow-up. Of the six patients with induced polymorphic ventricular tachycardias or ventricular fibrillation (none of whom experienced in-hospital drug-related cardiac arrest), one (17%) died suddenly during follow-up. Three extrastimuli were required to induce the baseline sustained arrhythmia in five of the eight patients with sudden death or cardiac arrest during follow-up. No patient with only nonsustained ventricular tachycardia induced at baseline study died suddenly or had a cardiac arrest during follow-up.

Nonsudden cardiac death occurred in 10 patients during follow-up. There were no significant differences between the three treatment groups with regard to the occurrence of nonsudden cardiac death—seven of 57 patients (12%) had no inducible sustained ventricular arrhythmias; one of 20 patients (5%) had inducible sustained arrhythmias suppressed on discharge therapy; and two of 20 patients (10%) had persistently inducible sustained arrhythmias on discharge therapy. Four additional patients died of noncardiac causes (sepsis, two; lung cancer, one; intracerebral hemorrhage, one). Total cardiac mortality rates for the entire study population (sudden and nonsudden deaths) were 16% at 1 year and 29% at 2 years.

**Discussion**

The results of this study indicate that electrophysiological testing provides an extremely useful tool for stratifying risk and predicting therapeutic efficacy in patients with asymptomatic nonsustained ventricular tachycardias, impaired ventricular function, and chronic coronary artery disease. Patients without baseline inducible sustained arrhythmias had a low probability of subsequent sudden death or cardiac arrest (2-year actuarial risk, 6%) without specific antiarrhythmic therapy, despite severe impairment of ventricular function and regardless of the findings on ambulatory monitoring.

In patients with baseline inducible sustained arrhythmias, effective suppressive therapy defined by electrophysiological testing could be identified in 50% of patients, and long-term treatment based on these results was associated with a similarly low incidence of sudden death. In contrast, discharge on drug therapy predicted to be ineffective was associated with an extremely high risk of future sudden death or cardiac arrest (34% at 1 year and 50% at 2 years). Of importance, the results of electrophysiological testing were relatively specific for predicting arrhythmic events; noncardiac deaths were similar in the three patient groups.

**Relation to Previous Investigations**

Several previous investigators have examined the role of electrophysiological testing in patients with nonsustained ventricular tachycardias. However, in each of these studies, 30–50% of patients had ejection fractions of more than 40%. Such patients were found to have an extremely low risk of sustained ventricular arrhythmias or sudden death during follow-up, which is consistent with the results of several recent large-scale epidemiological studies. For these reasons, only patients with impaired ventricular function were entered into our study protocol. In addition, we excluded patients without coronary artery disease because previous data indicate that electrophysiological testing may be less predictive in such patients, particularly in those with nonischemic cardiomyopathies.

Appropriate end points for the stimulation protocol in this patient population have not been universally adopted. Only two previous investigations were limited to patients with chronic coronary artery disease. In these studies, as well as the present study, the stimulation protocol included as many as three ventricular extrastimuli delivered at two right ventricular sites. The incidence of inducible sustained monomorphic ventricular tachycardia was similar in three studies—17 of 40 patients (43%) in the study of Klein and Machell, 24 of 62 patients (39%) in the study of Buxton et al, and 37 of 100 patients (37%) in the present study. Similar to the
findings of Buxton and colleagues, the majority of baseline sustained ventricular arrhythmias in the present study were initiated by three extrastimuli, and the majority of sudden deaths occurred in this subgroup. An optimal stimulation protocol in this patient population should probably include three extrastimuli.

The significance of induced sustained polymorphic arrhythmias is less clear. Available data indicate that such arrhythmias may be without prognostic significance in patients with no prior history of sustained ventricular arrhythmias, particularly when initiated by aggressive stimulation techniques. Only one of six patients with inducible sustained polymorphic tachycardias in the present study and none of four patients in the study of Buxton et al died suddenly. Based on these findings, it may be reasonable to withhold drug therapy in such patients.

We did not treat any patient with only inducible nonsustained ventricular tachycardia at the baseline study, regardless of duration or morphology. None of these 18 patients have had a sustained ventricular arrhythmia or sudden death during follow-up. In contrast, three of 15 patients of Buxton et al and one of nine patients of Klein and Machell with inducible nonsustained ventricular tachycardias died suddenly. Because many of these latter patients were treated with empiric antiarrhythmic therapy, proarrhythmic events may have contributed to the incidence of sudden death. Other studies with less aggressive stimulation techniques also reported sudden deaths during follow-up in patients with inducible nonsustained ventricular tachycardias. However, failure to use three extrastimuli significantly diminishes the predictive power of electrophysiological testing in this population.

An important difference between this and previous studies investigating the role of electrophysiological testing in patients with nonsustained ventricular tachycardias is the uniformity of patient treatment and follow-up. In previous studies, 30–40% of patients received empiric or Holter-guided antiarrhythmic therapy, regardless of the findings of electrophysiological testing. These patients experienced a disproportionately high incidence of subsequent sudden death or sustained ventricular arrhythmias during follow-up. Although the investigators concluded that electrophysiologically directed therapy was superior to nondirected therapy, assignment to treatment was not random. In both studies, the nondirected group included a significantly greater proportion of patients whose inducible ventricular arrhythmias could not be suppressed by drug therapy.

The results of this study help clarify the predictive role of electrophysiological testing in patients with inducible sustained ventricular arrhythmias. The suppression of these arrhythmias is associated with a good prognosis during 2-year follow-up. In patients in whom effective suppressive therapy could not be identified, we attempted to select therapy resulting in a slower and better-tolerated induced arrhythmia, based on guidelines suggested for electrophysiological testing in patients with spontaneous sustained ventricular arrhythmias. Despite these attempts, there were five sudden deaths and two nonfatal cardiac arrests in the 20 nonsuppressed patients during follow-up. This extremely poor outcome is compatible with the previously reported poor prognosis of "unguided" therapy.

Proarrhythmic Effect of Antiarrhythmic Therapy

An important finding was the frequent occurrence of spontaneous life-threatening proarrhythmic events during serial drug testing (7% of patients). While the facilitation of sustained arrhythmias after initiation of antiarrhythmic therapy for nonsustained ventricular tachycardia has been previously reported, no data are available regarding the frequency of spontaneous cardiac arrest in patients with nonsustained ventricular tachycardias undergoing serial electropharmacological testing. We were unable to identify predisposing factors that distinguished such patients from those without proarrhythmic events. While we chose to withdraw such patients from the study, it is conceivable that an effective drug may have been identified with additional drug testing.

Role of Ambulatory Monitoring and Clinical Variables in Selecting High-Risk Patients

No clinical or electrocardiographic data obtained before electrophysiological testing were useful in predicting the induction of sustained ventricular arrhythmias. Previous studies in more heterogeneous populations with spontaneous nonsustained ventricular tachycardias indicated that patients with coronary disease, previous myocardial infarction, and poor ventricular function have the greatest incidence of inducible ventricular arrhythmias; these characteristics were present in all of our study patients by design. Our results also suggest that ambulatory monitoring contains little additional information that is useful in predicting the induction of sustained ventricular arrhythmias in the laboratory.

While a greater length of spontaneous nonsustained ventricular tachycardia was more frequently associated with the occurrence of sudden death or cardiac arrest, both the induction of sustained ventricular arrhythmias at baseline electrophysiological study and the persistence of inducible ventricular arrhythmias on discharge therapy were more powerful predictors of outcome. Thus, prediction of sudden death on the basis of spontaneous arrhythmia characteristics (once the presence of nonsustained ventricular tachycardia is identified) is less useful than predictions based on the results of electrophysiological testing.

Limitations

The findings of this study are limited to patients with chronic coronary artery disease and impaired ventricular function and cannot be extrapolated to
patients with other forms of heart disease or to the convalescent phase of myocardial infarction or cardiac surgery. Although the present study establishes the benign prognoses of untreated patients who do not have inducible sustained arrhythmias, the true prognoses of patients with spontaneous asymptomatic nonsustained ventricular tachycardias and inducible sustained arrhythmias in the absence of drug therapy are unknown. It is possible that antiarrhythmic therapy may have contributed to the occurrence of sudden death and cardiac arrest during long-term follow-up in some of these patients. However, a similar incidence of sudden death in suppressed and nonsuppressed patients would have been expected.

The deleterious effects of some antiarrhythmic agents in patients with convalescent myocardial infarction and complex ventricular ectopy was demonstrated clearly by the preliminary results of the recent Cardiac Arrhythmia Suppression Trial. The findings of the present study support the prognostic use of electrophysiological testing in patients with nonsustained ventricular tachycardias, and confirms previous observations that amiodarone may provide incomplete protection from sudden death in patients with asymptomatic nonsustained ventricular tachycardias. A longer loading period for oral amiodarone may have improved suppression of ventricular arrhythmias. However, several recent reports support the prognostic use of electrophysiological testing in patients presenting with sustained ventricular arrhythmias after a total loading dose similar to that used in the present study.

Alternatively, failure to suppress inducible sustained ventricular arrhythmias may simply be a marker for subsequent high risk of spontaneous sustained arrhythmias. However, suppressed and nonsuppressed patients had similar ejection fractions, and only the persistence of inducible ventricular arrhythmias in a patient on antiarrhythmic therapy was an independent predictor of risk.

Clinical Implications

The findings of this study support previous observations that electrophysiological testing is useful in stratifying risk in patients with spontaneous nonsustained ventricular tachycardias and chronic coronary artery disease. Furthermore, these findings are valid even in a select population of patients with impaired ventricular function who are at the greatest risk of subsequent sudden death. Prophylactic therapy may be appropriately withheld in such patients without inducible sustained ventricular arrhythmias. However, electrophysiological guided pharmacological therapy in patients with inducible sustained ventricular arrhythmias may provide a more adequate and generalized test of the "electrophysiological guided treatment" hypothesis in this patient population and merits further consideration in the design of future clinical trials.

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**KEY WORDS** • ventricular tachycardia • sudden death • programmed electrical stimulation
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