Failure of Ambulatory Electrocardiographic Monitoring to Predict Results of Programmed Electrical Stimulation*  
Studies in Patients with Clinical Ventricular Tachyarrhythmias

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To test for an association between the results of ambulatory electrocardiographic monitoring (AEM) and programmed electrical stimulation (PES), or whether other factors better predict the results of PES, 57 patients (36 male and 21 female patients) presenting with either ventricular fibrillation (49 percent; 28/57) or sustained ventricular tachycardia (51 percent; 29/57) were studied. Each patient underwent AEM and PES using up to three ventricular extrastimuli. Sixty-three percent (36/57) had coronary disease; and of these, ventricular tachycardia was present during AEM in 64 percent (23/36) and induced by PES in 78 percent (28/36). With the addition of patients with other cardiac diagnoses, the results were 58 percent (33/57) and 60 percent (34/57), respectively. No AEM variable was positively associated with inducible ventricular tachycardia, including frequency of ventricular premature depolarizations, multiformity, couplets, or ventricular tachycardia. Clinical variables positively associated with inducible ventricular tachycardia were coronary disease, previous myocardial infarction, left ventricular dysfunction, male sex, and a history of recurrent arrhythmia. Therefore, clinical characteristics are more useful for predicting the results of PES than information derived from AEM.

Ambulatory electrocardiographic monitoring (AEM) and programmed electrical stimulation (PES) are two methods often employed in the evaluation of patients with known or suspected ventricular tachyarrhythmias. Ambulatory electrocardiographic monitoring is noninvasive, inexpensive, and widely available, as opposed to PES, which is invasive, generally more expensive, and restricted in its availability. Frequently, patients with cardiac arrhythmias are subjected to both forms of testing. If there exists a well-defined relationship between the results of AEM and PES, patients could be evaluated with confidence noninvasively, or at least screened for those most appropriate for PES. Recent studies have addressed whether specific factors derived from AEM might predict the results of PES; however, this association has not been verified in a homogeneous group of subjects with clinically documented sustained ventricular tachyarrhythmias, the group most likely to undergo PES. We sought to define the relationship between spontaneous arrhythmia detected during AEM and the results of PES in a series of patients with sustained ventricular tachyarrhythmias. We attempted to obtain both tests for all patients with sustained ventricular tachycardia or ventricular fibrillation referred to our institution over a four-year period. The data derived from AEM, along with other clinical information, were retrospectively analyzed to assess their usefulness in predicting the results of PES.

Materials and Methods

Patients

Between November 1982 and December 1986, there were 76 consecutive patients referred for evaluation of ventricular fibrillation or sustained ventricular tachycardia not associated with a reversible cause or acute myocardial infarction. An interview and a review of previously charted information were accomplished for each patient. No patient underwent the testing described in this report was tested during therapy with antiarrhythmic drugs. In patients previously treated with antiarrhythmic drugs, these were withheld for at least 48 hours or four half-lives prior to baseline testing. Subsequently, baseline testing, which included AEM and PES, was then performed. There were 57 patients (75 percent) who underwent both AEM and PES while not receiving antiarrhythmic drugs (baseline) who form the basis of this report. The remaining 19 patients were excluded from analysis because they did not have one of the methods of evaluation. Of these, five patients had incessant or unstable ventricular tachycardia and could not be withdrawn from therapy, three patients had been receiving long-term therapy with amiodarone at the time of referral, nine patients did not undergo complete PES, and in two patients, no baseline AEM recording was available because of technical reasons.

The clinical characteristics of the patients are shown in Table 1. There were 36 male and 21 female patients ranging in age from 16 to 78 years (mean, 55 ± 14 years). Coronary disease was the most common underlying cardiac disorder. Thirty patients (53 percent) had left ventricular dysfunction, with the overall mean left ventricular ejection fraction being 42 ± 18 percent. Arrhythmias documented at presentation included ventricular fibrillation (49 percent; 33/67 patients) and ventricular tachycardia (45 percent; 30/67 patients), with two patients (3 percent) presenting with both ventricular tachycardia and fibrillation. Other clinical variables included left ventricular ejection fraction being 42 ± 18 percent. Arrhythmias documented at presentation included ventricular fibrillation (49 percent; 33/67 patients) and ventricular tachycardia (45 percent; 30/67 patients), with two patients (3 percent) presenting with both ventricular tachycardia and fibrillation. Other clinical variables included

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Cardiac disease

Coronary arterial disease 36 63
Previous MI 30 53
Myocardial disease 7 12
Valvular disease 2 4
Miscellaneous or none 12 21

Presenting arrhythmia

Ventricular fibrillation 28 49
Sustained VT 29 51
Left ventricular dysfunction

Ejection fraction ≤40 percent 30 53

*Mean age, 55 ± 14 years; and M/F ratio, 1.5:1.

1MI, Myocardial infarction; VT, ventricular tachycardia.

28/57) and sustained ventricular tachycardia (51 percent; 29/57).

Symptoms at initial presentation of the clinical arrhythmia included cardiac arrest in 29 patients, syncope in seven, and presyncope or palpitations in 21.

Definitions

Previously published definitions were used for ventricular tachycardia. Spontaneous or induced by PES. Ventricular tachycardia was defined using standard electrocardiographic criteria (ventricular rate greater than 100 beats per minute, with the duration of the QRS complexes greater than 120 ms) and, when possible, was confirmed by His bundle recordings. Spontaneous nonsustained ventricular tachycardia was defined as greater than or equal to three consecutive ventricular ectopic depolarizations lasting less than 30 seconds. Spontaneous sustained ventricular tachycardia was defined as lasting 30 seconds or longer or requiring termination before that time because of hemodynamic compromise. Inducible ventricular tachycardia was defined as six or greater repetitive ventricular responses to extrastimulation.

Ambulatory Electrocardiographic Monitoring

An attempt was made to obtain at least one 24-hour ambulatory electrocardiographic recording for each patient. Thirty-five patients had one day of recording, and 22 had more than one day of recording. The mean number of recorded hours was 30 ± 11. Tapes were analyzed with a computer-aided scanner (Marquette Electronics, Inc). All patients had full disclosure printouts which were reviewed in full by one of us to assess the presence and frequency of ventricular tachycardia. The internal reproducibility of our laboratory, determined by repeated analysis of randomly selected tapes, was 99.5 percent for total beats, 96.2 percent for ventricular premature depolarizations, 85.2 percent for ventricular couplets, and 97.1 percent for ventricular tachycardia.

Programmed Electrical Stimulation

Following informed consent, each of the patients had baseline invasive cardiac electrophysiologic testing in the fasting nonsedated state. Programmed electrical stimulation was performed using a constant current stimulator (Bloom Ltd). All patients were tested using rectangular pulses of 2 ms duration at 2.5 times middiastolic threshold. Programmed electrical stimulation involved the introduction of initially one, then two, and finally three ventricular extrastimuli during ventricular pacing at cycle lengths of 600, 500, or 400 ms. Ventricular extrastimuli were started in middiastole and decrementally advanced to refractoriness (with the exception of Sn, which was not decremented beyond 200 ms). If ventricular tachycardia was not induced at the right ventricular apex, the protocol was repeated at the right ventricular outflow tract. All patients with negative test results were studied at two right ventricular sites. The first 11 noninducible patients were tested with one drive cycle length, while the latter 12 were tested with two drive cycle lengths. To be considered positive, the morphology of the induced ventricular arrhythmia had to match the clinical morphology (when known) and be at least six beats in duration.

Statistical Analysis

Continuous data are presented as the mean ± standard deviation. Univariate analysis was carried out using Fisher's exact test. Student's two-tailed t-test for independent groups was used to analyze continuous data. The log transformed values were used when they produced a more normal distribution. Alpha was considered significant at 0.05.

RESULTS

Programmed electrical stimulation induced ventricular tachyarrhythmia (Esix beats) in 28 (78 percent) of 36 patients with coronary disease, and 34 (60 percent) of 57 total patients. Of the 34 patients with inducible ventricular tachyarrhythmias, 24 had inducible sustained monomorphic ventricular tachycardia, seven had inducible ventricular fibrillation or polymorphic ventricular tachycardia, and three had nonsustained ventricular tachycardia. Of the 24 patients with inducible monomorphic ventricular tachycardia, 17 (71 percent) had a history of sustained ventricular tachycardia, and seven (29 percent) had a history of ventricular fibrillation. In the seven patients with inducible ventricular fibrillation or polymorphic ventricular tachycardia, the clinical arrhythmia was ventricular fibrillation in six and sustained ventricular tachycardia in one. Nonsustained ventricular tachycardia was the end point for stimulation in only three patients, and the clinical arrhythmia was ventricular fibrillation in two and sustained ventricular tachycardia in one.

A number of clinical variables were significantly associated with the results of PES (Table 2). These included coronary disease, previous myocardial infarction, male sex, left ventricular dysfunction, and a history of more than one documented occurrence of the clinical arrhythmia. Neither age nor the type of

Table 2—Clinical Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-inducible</th>
<th>Inducible</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Continuous variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>52 ± 15</td>
<td>57 ± 14</td>
<td>0.19</td>
</tr>
<tr>
<td>Ejection fraction, percent</td>
<td>49 ± 19</td>
<td>39 ± 15</td>
<td>0.05*</td>
</tr>
<tr>
<td>Discrete variables</td>
<td></td>
<td></td>
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<tr>
<td>Male sex</td>
<td>10/23</td>
<td>26/34</td>
<td>0.01*</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>8/23</td>
<td>28/34</td>
<td>0.0004*</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4/23</td>
<td>26/34</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Ejection fraction ≤40 percent</td>
<td>9/22</td>
<td>21/33</td>
<td>0.16</td>
</tr>
<tr>
<td>History of sustained VT</td>
<td>10/23</td>
<td>19/34</td>
<td>0.42</td>
</tr>
<tr>
<td>Recurrent arrhythmia</td>
<td>8/23</td>
<td>28/34</td>
<td>0.0004*</td>
</tr>
</tbody>
</table>

*p<0.05.

†VT, Ventricular tachycardia.
presenting rhythm (ventricular fibrillation or sustained ventricular tachycardia) was predictive of the results of PES. Additional factors that were analyzed and not found to be associated with the results of PES were variables at the time of the initial sustained arrhythmia, including serum potassium level, corrected Q-T interval, or antiarrhythmic drug therapy.

Patients were studied with AEM for a mean of 30 ± 11 hours. Twenty-two patients had more than one 24-hour monitor placed. Of these, there was concordance between the different days of monitoring for the presence of ventricular tachycardia in 68 percent (15 patients), the presence of couplets in 82 percent (18 patients), and in the hourly frequency of ventricular premature depolarizations (mean ±30) in 82 percent (18 patients). Table 3 displays information derived from AEM and its relation to the results of PES. Neither the frequency of ventricular premature depolarizations nor the presence of any of the types of complex arrhythmia (multiformity, couplets, or ventricular tachycardia) was associated with inducible ventricular tachycardia.

A separate analysis of patients with underlying coronary disease was also performed. Again, clinical variables associated with inducible ventricular tachycardia were left ventricular dysfunction and a history of multiple occurrences of the sustained clinical arrhythmia (Table 4). Factors which were likely a function of the presence of coronary disease, such as male sex and previous myocardial infarction, no longer reached statistical significance. The results of AEM again failed to predict the results of PES in these patients (Table 5).

Table 6 delineates the sensitivity, specificity, and positive predictive value of different variables for predicting inducible ventricular tachyarrhythmias in a selected population of patients with clinically sustained ventricular tachyarrhythmias. The most significant factors were clinical variables. Variables derived from AEM again proved to be poor predictors.

**DISCUSSION**

Ambulatory electrocardiographic monitoring has been extensively used to evaluate patients with cardiac arrhythmias.1 It is widely available and noninvasive and has been shown to provide useful prognostic information in patients with a history of myocardial infarction or congestive heart failure.10-12 Some investigators have used AEM to evaluate patients with a
history of life-threatening arrhythmias and to guide subsequent antiarrhythmic drug therapy. However, other investigators have demonstrated significant variability in the frequency of spontaneous arrhythmias as detected by AEM and have questioned the reliability of this method for managing life-threatening arrhythmias. Since even normal subjects often have ventricular arrhythmias detected by AEM and since these individuals have been shown to have a low probability of subsequent clinical arrhythmias, the clinical setting seems to be an important addition to the data derived from AEM in its ability to predict subsequent outcome.

Programmed electrical stimulation has also been shown to be useful in evaluating patients with life-threatening cardiac arrhythmias. Ventricular tachycardia inducible by PES has been generally predictive of subsequent morbidity clinical events. Vandepol et al. found that while inducible ventricular tachycardia was commonly found in patients in whom the rhythm was present clinically, it was rarely induced in patients without a history of ventricular tachycardias. Richards et al. tested 165 patients following myocardial infarction and found a higher incidence of subsequent sudden death in patients with inducible ventricular tachycardias; however, PES is invasive, expensive, and more limited in its availability than AEM. It would therefore be desirable to be able to screen patients noninvasively for those most likely to benefit from PES.

The ability to induce ventricular tachycardia with PES relates in part to the presence and type of underlying heart disease. Skale et al. showed that in survivors of cardiac arrest, ventricular tachycardia was inducible in 86 percent of the patients with coronary disease, but in only 63 percent of those without coronary disease. In a study by Naccarelli et al., ventricular tachycardia was inducible in 69 percent of the patients who had ventricular tachycardia without underlying coronary disease. Other investigators have found an even lower incidence of inducible ventricular tachycardia in patients without coronary disease. The variation in results may be due to differences in the protocols for stimulation; however, regardless of the pacing protocol, ventricular tachycardia is more commonly induced in those patients with underlying coronary disease than in those patients without it. The results of the current study are in agreement with this finding. We found the most useful predictors to be the presence of coronary disease, myocardial infarction, male sex, and a history of recurrent clinical arrhythmic events. Male sex likely reflects the higher incidence of coronary disease among male subjects, rather than independent information. Patients with impaired left ventricular function were significantly more likely to be inducible, regardless of the presence of coronary disease. The results of this study therefore suggest that clinical factors are important for determining the results of PES.

In evaluating a heterogeneous group of subjects, Gradman et al. suggested that spontaneous and induced ventricular arrhythmias were related in definable ways and that certain complex ectopic features were correlated with ventricular inducibility by PES. These investigators found that a ventricular premature complex frequency of greater than 100/1,000 normal beats, a couplet frequency greater than 1/1,000 normal beats, and an index derived from a ratio of ventricular couplets to initial premature ventricular complexes (repetition index ≥15) were predictive of inducibility; however, in the current study, none of the variables derived from AEM could be positively correlated with the results of PES. There are a number of possible reasons for this disparity. The study by Gradman et al. was limited by a number of factors. These investigators used a short period of recording (mean, 13.8 hours), some patients were receiving antiarrhythmic drugs at the time of evaluation, and only 46 percent of their patients were evaluated for a sustained ventricular tachyarrhythmia. The majority of the remainder were evaluated for unexplained syncope, a group with neither frequent baseline arrhythmia nor a high frequency of inducible ventricular tachycardia by PES. In the current study, analysis was restricted to only those patients with clinically documented sustained ventricular tachyarrhythmias. Patients were subjected to substantially longer periods of monitoring (mean, 30 hours). Additionally, only patients not receiving antiarrhythmic drugs were analyzed, in order to avoid the effect of medications. Each of these factors should have aided in uncovering a more substantial amount of spontaneous arrhythmia. Additionally, the results of AEM should be a more accurate reflection of the baseline clinical state when evaluated without antiarrhythmic drug therapy.

Pratt et al. also compared AEM and PES but found

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<tr>
<th>Table 6—Sensitivity, Specificity, and Positive Predictive Value of Various Factors for Inducible Ventricular Tachyarrhythmia Given a History of Life-Threatening Ventricular Arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data</strong></td>
</tr>
<tr>
<td>Previous MI</td>
</tr>
<tr>
<td>Recurrent arrhythmia</td>
</tr>
<tr>
<td>CAD</td>
</tr>
<tr>
<td>EF ≥40 percent</td>
</tr>
<tr>
<td>VT on monitoring</td>
</tr>
<tr>
<td>Repetition index ≥15</td>
</tr>
</tbody>
</table>

*M* Myocardial infarction; CAD, coronary arterial disease; EF, left ventricular ejection fraction; and VT, ventricular tachycardia.
that there was no single or combined AEM criteria that predicted inducibility. A majority of the patients in their study had clinically documented ventricular tachyarrhythmias, although 14 percent were evaluated for syncope of unknown cause. In 12 of 53 subjects, four extrastimuli or ventricular burst pacing was required to induce ventricular tachycardia. These techniques have previously been reported by these same authors to produce previously undocumented ventricular tachycardia in up to 48 percent of subjects.24 While the investigators found that none of the AEM criteria that they analyzed predicted the results of PES, the presence of coronary disease and a left ventricular ejection fraction of 30 percent or less were predictive of inducibility. The results of the current study agree with these findings.

The results of this study should be interpreted with caution. The limited size of the sample, while comparable to that of other similar studies, increases the probability of type 2 error. Additionally, variations in protocols for PES make results of electrophysiologic studies done at different testing centers difficult to compare. The incidence of inducible ventricular tachycardia in this study was somewhat lower than in some other reports.7-10 This may be due in part to the fact that the pacing protocol was designed to avoid induction of nonclinical arrhythmias. This was accomplished by limiting testing to three extrastimuli at only 2.5 times threshold and by not programming any Si extrastimulus at less than a 200-ms interval.25 Finally, this study was not meant to select the best method of evaluating patients with life-threatening ventricular arrhythmias. Rather, this study demonstrates that the results of AEM and PES are often discordant. The most important factors in predicting inducible ventricular tachycardia by PES are clinical factors. While the results of AEM do not appear to predict the results of PES in a subgroup of patients with a history of life-threatening ventricular arrhythmia, this does not suggest that it is not useful in managing many patients. Neither AEM nor PES identifies ventricular tachycardia at baseline in all patients with a previous history of serious arrhythmias, highlighting the difficulty in managing this type of patient.

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