Results and Efficiency of Programmed Ventricular Stimulation With Four Extrastimuli Compared With One, Two, and Three Extrastimuli

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Background  Conventional programmed ventricular stimulation protocols are inefficient compared with more recently proposed protocols. The purpose of the present study was to determine if additional efficiency could be derived from a 6-step programmed ventricular stimulation protocol that exclusively uses four extrastimuli.

Methods and Results  The subjects were 209 consecutive patients with coronary artery disease and documented sustained monomorphic ventricular tachycardia, nonsustained ventricular tachycardia, aborted sudden death, or syncope. These patients underwent 159 electrophysiological tests in the absence of antiarrhythmic drug therapy and 105 electrophysiological tests in the presence of antiarrhythmic therapy. Programmed stimulation was performed with two protocols in random order in each patient. Both protocols used an eight-beat drive train, 4-s intertrain pause, and basic drive cycle lengths of 350, 400, and 600 ms. The 6-step protocol started with coupling intervals of 290, 280, 270, and 260 ms, which were shortened simultaneously in 10-ms steps until S2 was refractory. The 18-step protocol used one, two, and three extrastimuli in conventional sequential fashion. The end points were 30 s of sustained monomorphic ventricular tachycardia, two episodes of polymorphic ventricular tachycardia requiring cardioversion, or completion of the protocol at two right ventricular sites. There was no significant difference in the yield of sustained monomorphic ventricular tachycardia using the two protocols, regardless of the clinical presentation or treatment with antiarrhythmic drugs. Polymorphic ventricular tachycardia occurred with the 18-step protocol twice as frequently as with the 6-step protocol (6% versus 3%, P<.001). The duration of the 18-step protocol was significantly longer than that of the 6-step protocol in patients with inducible ventricular tachycardia (5.5±7 versus 2.3±2 minutes, P<.001), as well as in patients without inducible ventricular tachycardia (25.4±7 versus 6.9±2 minutes, P<.001).

Conclusions  A stimulation protocol that exclusively uses four extrastimuli improves the specificity and efficiency of programmed ventricular stimulation without compromising the yield of monomorphic ventricular tachycardia in patients with coronary artery disease. (Circulation. 1994;90:2827-2832.)

Key Words  • test • electrophysiology • stimulation • tachycardia

Methods

Patient Characteristics

The subjects of this study were 209 consecutive patients with coronary artery disease who underwent an electrophysiological test for evaluation of sustained monomorphic VT (79 patients), nonsustained VT (69 patients), aborted sudden death with ventricular fibrillation (VF) noted at the time of resuscitation (30 patients), or unexplained syncope (31 patients). Each patient had a history of transmural myocardial infarction or coronary artery disease documented by cardiac catheterization. There were 169 men and 40 women with a mean age of 62±10 years (±SD). The mean left ventricular ejection fraction (LVEF) was 0.32±0.13. One hundred forty-two of the patients (68%) had a LVEF of less than 0.40. A total of 159 patients underwent a baseline electrophysiological test in the absence of antiarrhythmic medications, and 50 patients underwent initial testing while being treated with an antiarrhythmic drug. Among the 209 patients, 40 patients underwent a total of 55 additional electrophysiological tests to assess drug efficacy, resulting in a total of 264 electrophysiological tests. Amiodarone was the most commonly used drug, with class IA agents or sotalol being the next most frequently used (Table 1).

An additional group of 28 patients (13 men and 15 women; mean age, 39±12 years) without structural heart disease served as a control group for the 6-step protocol. These patients, who were all undergoing electrophysiological testing for the evaluation of paroxysmal supraventricular tachycardia,
TABLE 1. Antarrhythmic Agents Used During Electropharmacological Testing

<table>
<thead>
<tr>
<th>Antiarrhythmic Agent</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>66 63</td>
</tr>
<tr>
<td>IA agents (procainamide, quinidine)</td>
<td>18 17</td>
</tr>
<tr>
<td>Sotalol</td>
<td>8 8</td>
</tr>
<tr>
<td>Combination</td>
<td>8 8</td>
</tr>
<tr>
<td>Mexilitine</td>
<td>3 2</td>
</tr>
<tr>
<td>Propafenone</td>
<td>1 1</td>
</tr>
<tr>
<td>Ethmozine</td>
<td>1 1</td>
</tr>
</tbody>
</table>

also underwent programmed ventricular stimulation with the 6-step protocol.

Electrophysiological Testing

All patients underwent right programmed ventricular stimulation in a postabsorptive state after informed consent was obtained. Patients studied at baseline (without antiarrhythmic therapy) waited a minimum of five half-lives after cessation of drug therapy before undergoing programmed stimulation. Electropharmacological testing was performed two days after initiation of therapy with a IA agent, 7 to 10 days after initiation of amiodarone, and after achieving the maximum tolerated dose of sotalol (usually 240 mg BID).

Each patient underwent cannulation of the right femoral vein and placement of quadripolar pacing catheters in the high right atrium, across the tricuspid annulus in the His bundle position, and at the right ventricular apex. The intracardiac electrograms and leads V1, I, II, and III were displayed on an oscilloscope and recorded at a paper speed of 25 to 100 mm/s on a Mingograf 7 recorder (Siemens-Elema, Inc). PACing was performed with a programmable stimulator (Bloom Associates). The pacing stimuli had a duration of 2 ms and a current strength of two times the diastolic threshold, which was always less than 1 mA. A 12-lead ECG was recorded whenever sustained monomorphic VT was induced.

Study Protocol

Each patient underwent programmed stimulation of the right ventricle with both an 18-step protocol using one, two, and three extrastimuli and a 6-step protocol (Table 2). The order in which these two protocols were used was determined in random fashion. The only exception to this randomization was the control group of 28 patients with paroxysmal supraventricular tachycardia. This group underwent programmed ventricular stimulation only with the 6-step protocol.

The 18-step protocol has been previously described and validated. This protocol uses one, two, and three extrastimuli in sequential fashion following an eight-beat drive train. The 18-step protocol differs from most conventional protocols in that it uses increasing basic drive train cycle lengths of 350, 400, and then 600 ms.

The 6-step protocol uses exclusively four extrastimuli. At no point are one, two, or three extrastimuli used. At each basic drive train cycle length, programmed stimulation is initiated with coupling intervals of 290, 280, 270, and 260 ms for the first through fourth extrastimuli. With this protocol, the coupling intervals of the extrastimuli are shortened simultaneously in 10-ms steps until S2 is refractory or a 200-ms coupling interval is reached. If S2 is refractory at 290 ms, all extrastimuli are lengthened by 30 ms, and programmed stimulation is then initiated.

With both protocols, programmed stimulation was performed at the right ventricular apex and at either the right ventricular outflow tract or right ventricular septum. Coupling intervals were limited to a minimum of 200 ms to minimize induction of polymorphic VT. A 4-s pause was used between drive trains. Both protocols were timed with a stopwatch from the onset of programmed stimulation until an end point was

TABLE 2. Description of the Stimulation Protocols

<table>
<thead>
<tr>
<th>Step</th>
<th>Site*</th>
<th>18-Step Protocol</th>
<th>Site*</th>
<th>6-Step Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>350 1</td>
<td>1</td>
<td>350 4</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>350 2</td>
<td>1</td>
<td>400 4</td>
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<tr>
<td>3</td>
<td>1</td>
<td>350 3</td>
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<tr>
<td>6</td>
<td>1</td>
<td>400 3</td>
<td>2</td>
<td>600 4</td>
</tr>
</tbody>
</table>

*Site 1 was the right ventricular apex; site 2 was the right ventricular outflow tract or septum. BDCL indicates basic drive cycle length (in ms); ES, no. of extrastimuli.
achieved and all timing was suspended for catheter manipulation. End points in the absence of antiarrhythmic drug therapy were the reproducible induction of 30 s or more of monomorphic VT, two episodes of polymorphic VT or VF requiring cardioversion, or noninducibility at two right ventricular sites. End points during antiarrhythmic drug therapy consisted of the reproducible induction of 15 beats or more of monomorphic VT, two episodes of polymorphic VT or VF requiring cardioversion, or noninducibility at two right ventricular sites.

Definitions
Sustained VT/VF was defined as VT/VF lasting more than 30 s or requiring termination because of hemodynamic collapse. An arrhythmia was considered nonsustained if it was six beats to 30 s in duration. VT was defined as monomorphic if the QRS configuration was constant in all leads and the VT cycle length was more than or equal to 230 ms. Polymorphic VT was defined as VT in which the QRS morphology was variable from beat to beat in at least one of the ECG leads. For the purpose of this study, no attempts were made to distinguish polymorphic VT, ventricular flutter, and VF; all induced ventricular arrhythmias that were sustained and polymorphic or had a cycle length of less than 230 ms were classified as sustained polymorphic VT. Sustained monomorphic VT was considered a clinical end point regardless of the documented clinical morphology.

Statistical Analysis
Statistical comparisons among groups were performed using Student’s t test. Comparisons between two or more variables within the two groups were performed using contingency table analysis. A value of $P<.05$ was considered significant.

Results

Pooled Results
Among 264 electrophysiological tests, sustained monomorphic VT was the only arrhythmia induced in 132 cases using the 18-step protocol and in 133 cases using the 6-step protocol ($P=1.0$). Polymorphic VT and sustained monomorphic VT were both induced in two cases using the 18-step protocol and in one case using the 6-step protocol. Overall, polymorphic VT was induced in 17 cases using the 18-step protocol and in only 8 cases using the 6-step protocol ($P=.0001$). In 16 cases (6%), sustained monomorphic VT was induced by one protocol and not the other.

Patients Presenting With Sustained VT
Among 44 patients with a history of sustained monomorphic VT, sustained monomorphic VT was induced in the absence of antiarrhythmic drug therapy in 39 patients (89%) by the 18-step protocol and in 41 patients (93%) by the 6-step protocol ($P=.4$). One of the 5 patients in whom sustained monomorphic VT was not induced with the 18-step protocol had inducible polymorphic VT, and the other 4 patients had no inducible arrhythmias.

One patient with inducible sustained monomorphic VT during the 18-step protocol had no inducible VT with the 6-step protocol, and 3 patients with inducible sustained monomorphic VT using the 6-step protocol had no inducible VT with the 18-step protocol.

Patients Presenting With Nonsustained VT
Among the 63 patients who presented with nonsustained VT, the 18-step and 6-step protocols both induced sustained monomorphic VT in 8 of 63 patients (13%). Polymorphic VT was induced in 9 patients with the 18-step protocol (14%) and in 2 patients (3%) with the 6-step protocol ($P<.05$). Only 1 patient who had inducible monomorphic VT with the 18-step protocol did not have inducible monomorphic VT with the 6-step protocol, and only 1 patient who had inducible monomorphic VT with the 6-step protocol did not have inducible monomorphic VT with the 18-step protocol.

Patients Presenting With Aborted Sudden Death
Two of 26 patients (8%) presenting with aborted sudden death had inducible sustained monomorphic VT in the absence of antiarrhythmic drug therapy using both the 18-step and the 6-step protocols. The sustained monomorphic VT induced by the 18-step protocol had a mean cycle length of 318±70 ms compared with 320±71 ms for the 6-step protocol ($P=.8$). Polymorphic VT was induced in 3 of 26 patients (11%) with the 18-step protocol and in 4 of 26 patients (15%) with the 6-step protocol ($P=.7$). None of the patients had an arrhythmia inducible by one protocol and not the other.
Patients Presenting With Syncope

Among the 26 patients presenting with syncope, the 18-step protocol induced sustained monomorphic VT in 7 patients (27%), and the 6-step protocol induced sustained monomorphic VT in 6 patients (23%) \((P=.7)\). In 2 patients, sustained monomorphic VT was induced with the 18-step protocol but not the 6-step protocol, and in 1 patient, sustained monomorphic VT was induced with the 6-step protocol but not with the 18-step protocol. Polymorphic VT was induced in 2 patients with the 18-step protocol and in 0 patients with the 6-step protocol \((P=.15)\).

Results of Electropharmacological Testing

Seventy-nine patients underwent a total of 105 electrophysiological tests to assess the efficacy of antiarrhythmic therapy. The 18-step protocol induced sustained monomorphic VT in 78 patients (74%), and the 6-step protocol induced sustained monomorphic VT in 77 patients (73%) \((P=1.0)\). Polymorphic VT was induced in 2 patients with the 18-step protocol and in 1 patient with the 6-step protocol. In 4 patients, sustained monomorphic VT was induced with the 18-step protocol and not with the 6-step protocol, and in 3 patients sustained monomorphic VT was induced with the 6-step protocol and not with the 18-step protocol.

Control Patients

Among the 28 patients in the control group, nonsustained polymorphic VT was induced in 1 patient (3%). No other ventricular arrhythmias were induced in this group of patients.

Morphology of Induced Monomorphic VT

Among the 209 patients studied, the morphology of the clinically occurring sustained monomorphic VT was documented and available for review in 126 patients; this included all patients who presented with sustained monomorphic VT. The morphology of the clinically occurring sustained monomorphic VT was different than that of the induced VT in 13 patients (11%) using the 18-step protocol and in 7 patients (6%, \(P=.24\)) using the 6-step protocol. The clinically occurring and induced VTs had the same morphology in all of the patients who presented with sustained monomorphic VT in the absence of antiarrhythmic drug therapy.

Duration of Stimulation Protocols

The duration of the 18-step protocol was greater than the duration of the 6-step protocol under a variety of circumstances. When all patients with inducible sustained monomorphic VT were pooled, the mean time to induction with the 18-step protocol was 5.5±7 compared with 2.3±2 minutes with the 6-step protocol \((P<.001)\). There was a corresponding increase in the number of steps required to induce sustained monomorphic VT with the 18-step protocol (Fig 1). In the absence of antiarrhythmic therapy, induction of VT with the 6-step protocol required only 2.4±2.6 minutes compared with 6.9±8.3 minutes using the 18-step protocol \((P<.001)\). Induction of sustained monomorphic VT during antiarrhythmic therapy required a mean of 2.0±1.9 minutes using the 6-step protocol compared with 4.5±6.2 minutes using the 18-step protocol \((P<.001)\). In both subgroups of patients, the 18-step protocol required more steps to induce sustained monomorphic VT than did the 6-step protocol (Figs 2 and 3). In patients without inducible VT, the 18-step protocol required a mean of 25.4±7 minutes to complete compared with 6.9±2 minutes for the 6-step protocol \((P<.001)\).

Discussion

Main Findings

This study demonstrates that there is no significant difference in the yield of sustained monomorphic VT in patients undergoing programmed ventricular stimulation using the 6-step protocol described in this study in comparison to a more conventional 18-step protocol. Both protocols demonstrated equal sensitivity for the induction of VT in patients who presented with sustained monomorphic VT and underwent a baseline electrophysiological test in the absence of antiarrhythmic therapy. Furthermore, there was no significant difference in the cycle lengths of the tachycardias induced by the two protocols. Of importance is that the 18-step protocol was more likely to induce polymorphic VT than was the 6-step protocol. In the control group, the 6-step protocol induced polymorphic VT in only 1 patient, further validating its high degree of specificity. The 6-step protocol was significantly less time consuming in all patient subgroups, but especially in patients who did not have inducible VT. Therefore, the 6-step protocol described in this study can significantly improve the specificity and efficiency of programmed ventricular stimulation without compromising sensitivity.

Efficiency of the 6-Step Protocol

Conventional programmed stimulation protocols generally initiate extrastimulation during sinus rhythm and progress to shorter basic drive cycle lengths. Initiation of programmed ventricular stimulation beginning with the shortest drive cycle length and progressing to longer drive cycle lengths has been shown to decrease the time required to induce VT.13,15 Furthermore, the use of four extrastimuli has been shown to increase the yield of programmed stimulation by approximately 15%.16,17 The use of one and two extrastimuli accounts for only
15% to 20% of inducible VTs, and only a small percentage of these arrhythmias are not inducible with three extrastimuli. In prior studies, the majority of sustained monomorphic VTs were induced when the maximum number of extrastimuli accompanied the shortest drive cycle length. This combination is achieved in the first step of the 6-step protocol compared with the third step of the 18-step protocol, which affords a significant time advantage to the 6-step protocol. The 6-step protocol is more efficient because it begins with the pacing drive train–extrastimuli combination that is most likely to induce tachycardia. Furthermore, coupling intervals of the four extrastimuli are shortened in tandem rather than in sequence. These modifications resulted in a significant time savings. For example, when VT was not inducible, the 6-step protocol was completed a mean of 18 minutes earlier than the 18-step protocol.

Induction of Monomorphic VT

The results of programmed stimulation with the 6-step protocol correspond to the results that have been reported using widely accepted methodologies.1-4,18-21 With the 6-step protocol, there was induction of sustained monomorphic VT in 93% of patients with a documented episode of sustained monomorphic VT, which is comparable to the yield of protocols used in previous studies.

In patients with a LVEF less than 0.40 and nonsustained VT, the 6-step protocol induced sustained monomorphic VT in 20% of patients. In all patients with nonsustained VT, the yield was 13%. These induction rates are similar to the findings of some studies of programmed ventricular stimulation in patients with nonsustained VT and lower than in other such studies.2,22,23 The induction of sustained monomorphic VT in only 8% of the patients who presented with aborted sudden death is lower than in prior studies.24-25 Whereas the induction of sustained monomorphic VT in 23% of patients who presented with syncope of unknown etiology is similar to the results of prior studies.26 In patients undergoing electropharmacological testing, only 27% did not have inducible sustained monomorphic VT. This was the same degree of VT suppression found in this study with the 18-step protocol and in most prior studies.27,28

Induction of Polymorphic VT

Overall, polymorphic VT was induced more frequently with the 18-step protocol than with the 6-step protocol by a >2:1 margin, despite the fact that both protocols limited the shortest coupling interval to 200 ms.

Prior studies have indicated that the induction of polymorphic VT and VF increases with the number of extrastimuli.7,15 These studies were performed using much more repetitive stimulation protocols than the 6-step protocol. The less frequent occurrence of polymorphic VT with the 6-step protocol may be due to its shorter duration and less repetitive nature compared with the 18-step protocol. Prior studies have noted the importance of the repetitiveness of programmed stimulation in eliciting the different possible morphologies of inducible sustained monomorphic VT and in increasing the sensitivity of programmed stimulation for sustained monomorphic VT. Furthermore, a positive correlation has been noted between the number of programmed stimulation steps used and the induction of polymorphic VT.29 These findings, and the findings of the present study, suggest that the repetitiveness of pacing protocols plays a greater role than the number of extrastimuli in provoking the induction of polymorphic VT during programmed ventricular stimulation.

Study Limitation

To maintain a homogeneous patient population, this study was limited to patients with ischemic heart disease, with the exception of the control group. Therefore, the results may not apply to patients with other types of heart disease. In addition, the ability of the 6-step protocol to predict drug success or failure and the reproducibility of VT induction with this protocol have not been evaluated.

Conclusions

Compared with an 18-step protocol that sequentially uses one, two, and three extrastimuli, the 6-step protocol described in the present study improves the specificity and efficiency of programmed ventricular stimulation without compromising the yield of monomorphic VT in patients with coronary artery disease. Of note is that the 18-step protocol used in this study has been shown to be more efficient than conventional stimulation protocols.13 Therefore, the advantages of the 6-step protocol demonstrated in the present study would be even more apparent when compared with conventional protocols that initially deliver extrastimuli during sinus rhythm or during a relatively long basic drive cycle length. Although promising, the widespread clinical application of this protocol should be adopted cautiously until its clinical applicability has been verified.

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