A prospective comparison of triple extrastimuli and left ventricular stimulation in studies of ventricular tachycardia induction

Fred Morady, M.D., Lorenzo Di Carlo, M.D., Stuart Winston, D.O., Jesse C. Davis, M.D., and Melvin M. Scheinman, M.D.

ABSTRACT One hundred and one patients with sustained unimorphic ventricular tachycardia underwent programmed ventricular stimulation with one of two protocols. Fifty patients underwent programmed stimulation with protocol A, which consisted of burst overdrive pacing, single, double, and triple extrastimuli at the right ventricular apex, right ventricular outflow tract, or septum, and then at the left ventricular apex. Fifty-one patients underwent programmed stimulation with protocol B, which consisted of burst overdrive pacing, single and double extrastimuli at the right ventricular apex, right ventricular outflow tract or septum, and at the left ventricular apex, followed by triple extrastimuli at these sites. The stimulation protocol was continued until sustained ventricular tachycardia or rapid, polymorphic ventricular tachycardia greater than 10 sec in duration was induced. With protocol A, clinical and nonclinical ventricular tachycardia was induced in 76% and 36% of patients, respectively; with protocol B, clinical and nonclinical ventricular tachycardia was induced in 85% and 38% of patients, respectively. Direct-current countershock for sustained polymorphic ventricular tachycardia was required in 10% of patients studied under protocol A, compared with in 2% of patients studied under protocol B. With protocol A, near-maximal yield of induced clinical (72%) and nonclinical ventricular tachycardia (30%) was attained after the use of triple extrastimuli at the first stimulation site. The yield of stimulation at a second right ventricular site and of left ventricular stimulation was only an additional 2% each. With protocol B, triple extrastimuli increased the yield of induced clinical ventricular tachycardia from 61% to 85%. In patients with sustained unimorphic ventricular tachycardia undergoing programmed ventricular stimulation, the use of triple extrastimuli at the first stimulation site (protocol A) resulted in a high yield of induced clinical ventricular tachycardia early in the protocol, but at the cost of a significant yield of nonclinical ventricular tachycardia. In the patient who has documented ventricular tachycardia, protocol A may be suitable since the nonclinical arrhythmias that are induced will be readily identifiable as such. The initial use of burst overdrive pacing and single and double extrastimuli in the right ventricle (protocol B) will obviate the need for triple extrastimuli and left ventricular stimulation in 53% of patients and result in a low yield of nonclinical arrhythmias, especially those that are polymorphic (4%). Protocol B may therefore be preferable in patients with sustained but undocumented ventricular tachycardia, to minimize uncertainty regarding the clinical significance of induced tachycardia. However, triple extrastimuli will still be required to induce clinical ventricular tachycardia in 24% of patients, and the overall yield of nonclinical ventricular tachycardia is similar with protocols A and B. Circulation 70, No. 1, 52-57, 1984.

THE USE of triple extrastimuli and left ventricular stimulation during programmed ventricular stimulation has been found to increase the yield of inducible ventricular tachycardia in patients with sustained ventricular tachycardia, aborted sudden death, and unexplained syncope.1-6 Although triple extrastimuli are more effective than single or double extrastimuli in inducing clinical forms of ventricular tachycardia, they also more often result in the induction of nonclinical forms of ventricular tachycardia or ventricular fibrillation.1,7-9 These nonclinical arrhythmias may require termination by direct-current countershock, thereby increasing patient discomfort and, potentially, morbidity resulting from electrophysiologic testing. On the other hand, left ventricular stimulation has not been found to facilitate the induction of nonclinical arrhythmias in patients without documented or sus-
pected ventricular tachycardia; however, catheter manipulation within the left ventricle may increase the risk associated with electrophysiologic testing. To date there have been no studies comparing the relative value of triple extrastimuli and left ventricular stimulation during electrophysiologic testing.

The goal of this study was to compare, in a prospective fashion, the results of two stimulation protocols using triple extrastimuli and left ventricular stimulation in patients with documented sustained unimorphic ventricular tachycardia. In the first protocol, left ventricular stimulation was performed only after stimulation at two right ventricular sites with triple extrastimuli. In the second protocol, triple extrastimuli were administered only after single and double extrastimuli had been administered in the right and left ventricles. This comparison was performed to identify the protocol that maximized the induction of clinical forms of ventricular tachycardia and minimized the induction of nonclinical forms.

Methods

One hundred and one patients with sustained unimorphic ventricular tachycardia documented on a 12-lead electrocardiogram were studied prospectively. Their clinical features are described in table 1. Sixty-five of the patients were being treated with one or more antiarrhythmic drugs at the time they experienced sustained ventricular tachycardia. The mean cycle length of the tachycardia was 340 ± 77 msec (mean ± SD).

Electrophysiologic testing was performed in patients in the fasting, unsedated state after informed consent was obtained and at least four half-lives after all antiarrhythmic drug treatment had been stopped. Quadripolar electrode catheters were inserted percutaneously into a femoral vein and positioned across the tricuspid valve (to record the His bundle electrogram) and within the right ventricle. Left ventricular stimulation was performed with a bipolar or quadripolar electrode catheter inserted percutaneously into a femoral artery and positioned against or near the left ventricular apex. Intravenous heparin (4000 units) was administered to patients undergoing left ventricular stimulation. Patients in whom left ventricular stimulation was not feasible due to a prosthetic aortic valve or severe aortoiliac atherosclerosis were excluded from this study.

Surface electrocardiographic leads V1, I, and III, the His bundle electrogram, and ventricular electrograms were displayed on an oscilloscope and recorded with a VR-12 Electronics for Medicine recorder. Stimulation was performed with a programmable stimulator (Bloom Associates, Narberth, PA). The pacing stimuli were 2 msec in duration and 5 mA in strength. Programmed stimulation with 5 mA stimuli in subjects without documented or suspected ventricular tachycardia has been reported to result in a similar incidence of nonclinical arrhythmias as that with stimuli that are twice diastolic threshold in strength.1,7,8

The stimulation protocols used in this study consisted of the following pacing modes. Burst overdrive pacing was performed for 3 sec at cycle lengths of 400, 350, 300, 275, and 250 msec. Single extrastimuli (S2) were introduced after 5 beat drive trains (S1) (cycle lengths 500 and 400 msec) and diastole was scanned in 10 msec decrements to the point of ventricular refractoriness. Double extrastimuli (S2S3) were introduced with S2 initially positioned 30 msec beyond ventricular refractoriness and S1 initially positioned 300 msec beyond S2. When S2 no longer evoked a response, the S2S3 interval was decreased in 10 msec steps until S3 again evoked a response and S1 was moved closer to S2 until it again failed to evoke a response. This process was continued until S2 reached ventricular refractoriness. Triple extrastimuli (S2S3S4) were introduced with S2 and S3 positioned 30 msec beyond their points of ventricular refractoriness and with an initial S4 interval of 300 msec. S4 was moved closer to S3 in 10 msec steps until it no longer evoked a response. The S2S3 and S3S4 intervals were then shortened in 10 msec steps until S4 again evoked a response and the S3S4 interval was then shortened in 10 msec steps until S4 again failed to evoke a response. This process was continued until S3 and S4 reached their point of ventricular refractoriness.

The first 50 patients in this study underwent programmed stimulation with protocol A, which consisted of burst overdrive pacing and stimulation with single, double, and triple extrastimuli applied initially at the right ventricular apex, then at the right ventricular outflow tract or septum, and then at the left ventricular apex. The next 51 patients in this study underwent programmed stimulation with protocol B, which consisted of burst overdrive pacing, then stimulation with single and double extrastimuli performed at the right ventricular apex, then at the right ventricular outflow tract or septum, and then at the left ventricular apex. If necessary, triple extrastimuli were then introduced in sequence at the right ventricular apex, right ventricular outflow tract or septum, and left ventricular apex. Protocols A and B are outlined in table 2. All catheters were positioned under fluoroscopic guidance so that stimulation at a particular site was always performed from the same location.

In patients without coronary artery disease who did not have inducible ventricular tachycardia, the original stimulation protocol was repeated during an infusion of isoproterenol titrated to maintain a heart rate of 120 beats/min. However, in no patient did isoproterenol facilitate the induction of ventricular tachycardia by programmed stimulation. The results of programmed stimulation during isoproterenol infusion are therefore not described in the Results. Patients in whom ventricular tachycardia was induced by isoproterenol alone (without programmed stimulation) were not included in this study.

Sustained ventricular tachycardia was defined as ventricular tachycardia of more than 30 sec duration or requiring termina-

### TABLE 1

<table>
<thead>
<tr>
<th>Clinical features of 101 patients with sustained ventricular tachycardia</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62 ± 11^A</td>
<td>56 ± 14</td>
</tr>
<tr>
<td>Men/women</td>
<td>44/6</td>
<td>36/15</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>Congestive cardiomyopathy</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular dysplasia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ventricular tachycardiac cycle length (msec)</td>
<td>316 ± 68</td>
<td>353 ± 86</td>
</tr>
</tbody>
</table>

^A Mean ± SD.
tion by direct-current countershock or overdrive pacing. Non-
sustained ventricular tachycardia was defined as that 6 beats to
30 sec in duration that terminated spontaneously. Induced
ventricular tachycardia was described as “clinical” if it had the
same morphologic characteristics and axis as a patient’s sponta-
neous tachycardia, as evaluated by comparison of leads V1, I, and
III.

The following end points were used with both stimulation
protocols. The protocol was stopped when ventricular tachycardia
requiring termination by direct-current countershock was induced
or when hemodynamically stable sustained ventricular tachycardia
not requiring direct-current countershock was reproducibly induced.
The stimulation protocol was not stopped if nonsustained ventricular tachycardia was induced unless it was
rapid (cycle length <220 msec), polymorphic, and longer than 10 sec in duration.

Statistical comparisons were performed with Fisher’s exact
test, chi-square analysis, or with Student’s t test.

Results

No complications occurred in the patients who under-
went programmed stimulation with either protocol
A or B.

The overall results of programmed stimulation with
protocols A and B are summarized in table 3. Clinical
ventricular tachycardia was induced in 76% and 85%
of patients who underwent programmed stimulation
with protocols A and B, respectively (NS). Nonclini-
cal ventricular tachycardia was induced in a total of
36% and 38% of patients undergoing programmed
stimulation with protocols A and B, respectively (NS).
In 7% and 11% of patients studied under protocols A
and B, respectively, both clinical and nonclinical
forms of ventricular tachycardia were induced.

Triple extrastimuli were used in 54% of patients
studied under protocol A and in 39% of patients studied
under protocol B. Of note is that among patients studied under protocol A, five of 50 (10%) required
direct-current countershock for termination of poly-
morphic sustained ventricular tachycardia; the tachycardia was induced by triple extrastimuli in four of
these five patients and by double extrastimuli in one.

Only one of 51 patients (2%) studied under protocol B
required direct-current countershock because of polymorphic sustained ventricular tachycardia, and it was
induced by triple extrastimuli.

The cumulative yield of induced clinical and non-
clinical ventricular tachycardia in patients who under-
went programmed stimulation with protocol A is shown in
figure 1. The largest increments in yield occurred early in the stimulation protocol, with the use of
double and triple extrastimuli at the right ventricular
apex. After completion of stimulation at the right ven-
tricular apex and outflow tract or septum, clinical ventricular tachycardia was induced in 72% of patients
and nonclinical ventricular tachycardia in 36% (unimor-
phic in 14% and polymorphic in 22%). The yield with
left ventricular stimulation was very low, with clinical
ventricular tachycardia being induced in only one addition-
al patient (2%); left ventricular stimulation did not increase the yield of nonclinical ventricular tachycardia.

The cumulative yield of induced clinical and non-
clinical ventricular tachycardia in patients who under-
went programmed stimulation with protocol B is shown in
figure 2. After the completion of stimulation with
overdrive pacing and single and double extra-
stimuli at two right ventricular sites, the cumulative
yield of induced clinical ventricular tachycardia was
53% and the yield of nonclinical ventricular tachycardia
was 20% (unimorphic in 16% and polymorphic in
4%). Overdrive pacing and single and double extra-
stimuli in the left ventricle increased the yield of
induced clinical ventricular tachycardia by 8% (to 61%),
with a minimal increase in the yield of nonclinical

<p>| TABLE 3 |
| Induction of clinical and nonclinical ventricular tachycardia (VT) with protocols A and B (n = 50 and 51, respectively) |</p>
<table>
<thead>
<tr>
<th>Type of VT induced</th>
<th>Protocol A</th>
<th>Protocol B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical VT</td>
<td>38(76)%</td>
<td>43(85)%</td>
</tr>
<tr>
<td>Clinical VT only</td>
<td>31(62)</td>
<td>32(63)</td>
</tr>
<tr>
<td>Clinical and nonclinical VT</td>
<td>7(14)</td>
<td>11(22)</td>
</tr>
<tr>
<td>Unimorphic</td>
<td>2(4)</td>
<td>7(14)</td>
</tr>
<tr>
<td>Polymorphic nonsustained</td>
<td>5(10)</td>
<td>3(6)</td>
</tr>
<tr>
<td>Polymorphic sustained</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonclinical VT only</td>
<td>12(24)</td>
<td>7(14)</td>
</tr>
<tr>
<td>Unimorphic</td>
<td>6(12)</td>
<td>3(6)</td>
</tr>
<tr>
<td>Polymorphic nonsustained</td>
<td>1(2)</td>
<td>3(6)</td>
</tr>
<tr>
<td>Polymorphic sustained</td>
<td>5(10)</td>
<td>1(2)</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>1(2)</td>
</tr>
</tbody>
</table>

*There were no significant differences between protocol A and B with respect to the incidence of clinical or nonclinical ventricular tachycardia.

*Numbers in parentheses represent percentages.
ventricular tachycardia to 22%. After the completion of programmed stimulation with triple extrastimuli at three sites, there was an additional 24% yield of clinical ventricular tachycardia, for a total of 85%. With the use of triple extrastimuli the yield of nonclinical VT increased from 22% to 35% (unimorphic in 19% and polymorphic in 16%).

The results of programmed stimulation in patients with and without coronary artery disease are summarized in Table 4. Among the patients who had coronary artery disease, the yield of clinical ventricular tachycardia tended to be higher than in patients without coronary artery disease, regardless of which protocol was used (82% vs 58% for protocol A, and 91% vs 69% for protocol B); however, these differences did not reach statistical significance (p > .05).

Discussion

The results of this study demonstrate that the use of triple extrastimuli early in a stimulation protocol results in a near-maximal yield of induced clinical ventricular tachycardia at the first ventricular site that is stimulated (figure 1). On the other hand, when triple extrastimuli are used only after stimulation with overdrive pacing and single and double extrastimuli in the right and left ventricles, the maximum yield of induced clinical ventricular tachycardia is not attained until late in the stimulation protocol (figure 2). These findings indicate that triple extrastimuli are more effective in inducing clinical ventricular tachycardia than is left ventricular stimulation.

Although the use of triple extrastimuli early in a ventricular stimulation protocol may shorten the time needed to induce clinical ventricular tachycardia, this advantage is offset by a tendency to increase the yield of nonclinical ventricular tachycardia. If the end point of a stimulation protocol is the induction of ventricular tachycardia requiring direct-current countershock, the induction of nonclinical, polymorphic, sustained ventricular tachycardia by triple extrastimuli at the right ventricular apex may preclude the induction of clinical disease for protocol A or B.

\[ \text{TABLE 4} \]

Results of programmed stimulation with protocols A and B in patients with and without coronary artery disease (CAD)

<table>
<thead>
<tr>
<th>CAD</th>
<th>n</th>
<th>Induced ventricular tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Clinical</td>
</tr>
<tr>
<td>Protocol A</td>
<td>Yes</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>Protocol B</td>
<td>Yes</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>16</td>
</tr>
</tbody>
</table>

\(^a\)Numbers in parentheses are percentages.
\(^b\)There was no significant difference between the incidence of inducible ventricular tachycardia in patients with and without coronary artery disease for protocol A or B.
ventricular tachycardia by single or double extrastimuli at another stimulation site.

In patients without documented or suspected ventricular tachycardia who undergo programmed ventricular stimulation, single and double extrastimuli induce nonclinical ventricular tachycardia infrequently, whereas triple extrastimuli induce nonclinical tachycardia (usually polymorphic) in up to 45% of patients. Our results indicate that the higher yield of nonclinical ventricular tachycardia with triple than with double extrastimuli also occurs in patients who have documented sustained unimorphic ventricular tachycardia. The use of double extrastimuli at multiple ventricular sites increases the yield of induced clinical ventricular tachycardia (61%) compared with the yield obtained with the use of double extrastimuli at only the right ventricular apex (47%), thereby eliminating the need for triple extrastimuli in some patients and minimizing the risk of inducing a nonclinical arrhythmia.

Robertson et al. reported that 11% of patients with clinically documented sustained ventricular tachycardia required left ventricular programmed stimulation to initiate the tachycardia. However, right ventricular stimulation was performed in their patients with overdrive pacing and single and double extrastimuli, but not with triple extrastimuli. The results of this study demonstrate that when left ventricular stimulation is preceded by right ventricular stimulation at two sites with triple extrastimuli, the additional yield of clinical ventricular tachycardia induced by left ventricular stimulation is only 2%. Therefore, the use of triple extrastimuli in the right ventricle will often preclude the need for left ventricular stimulation. However, when left ventricular stimulation with double extrastimuli is preceded by stimulation with double extrastimuli at two right ventricular sites, the yield of induced clinical ventricular tachycardia increases by 8%.

Limitations. The design of this study precludes any conclusions regarding the true yield of induced ventricular tachycardia with each pacing modality at each stimulation site. Because the stimulation protocols were sequential in nature and were discontinued when one of the defined end points was reached, only the cumulative yield of the various pacing modalities and stimulation sites was determined.

In patients who have been documented to have sustained unimorphic ventricular tachycardia, induced polymorphic ventricular tachycardia is readily identifiable as a nonclinical arrhythmia. However, the clinical significance of the "nonclinical" unimorphic ventricular tachycardia may be unclear. Designation of induced ventricular tachycardia as nonclinical presupposes that all episodes of tachycardia that a patient has had have been documented on a 12-lead electrocardiogram. Because this was not the case in the patients in

![FIGURE 2. The cumulative yield of induced clinical and nonclinical ventricular tachycardia with protocol B in 51 patients with documented unimorphic ventricular tachycardia. OT = outflow tract; S = septum; other abbreviations are as in figure 1.](image-url)
this study, and because it is probable that at least some patients have ventricular tachycardia of more than one morphologic type, it is likely that, in some cases, induced unimorphic ventricular tachycardia designated as nonclinical was actually clinical. Because endocardial mapping was not routinely performed in our patients, we cannot rule out the possibility that varying exit points from one reentry circuit accounted for varying morphologic characteristics of unimorphic ventricular tachycardia induced by programmed stimulation. Moreover, prior studies have demonstrated that unimorphic ventricular tachycardia is rarely inducible in patients who have never had documented or suspected ventricular tachycardia. For these reasons, the 76% and 85% yields of clinical ventricular tachycardia induced by protocols A and B, respectively, are most likely underestimates.

To avoid precipitating angina pectoris, the stimulation protocols used in this study did not include the routine use of isoproterenol in patients who had coronary disease. Reddy and Gettes19 demonstrated that isoproterenol facilitated the induction of sustained ventricular tachycardia by programmed stimulation in nine of 11 patients with recurrent ventricular tachycardia in whom right ventricular stimulation with up to two extrastimuli failed to induce tachycardia. Although it is possible that the yield of induced clinical ventricular tachycardia in our study may have been increased by the routine use of isoproterenol, we found that the use of isoproterenol in patients without coronary artery disease did not facilitate the induction of ventricular tachycardia by programmed stimulation. This observation suggests that isoproterenol less often facilitates the electrical induction of ventricular tachycardia when the baseline stimulation protocol includes triple extrastimuli and left ventricular stimulation.

In patients with sustained unimorphic ventricular tachycardia who undergo programmed ventricular stimulation the use of triple extrastimuli at the first stimulation site (protocol A) has the advantage of resulting in a high yield of induced clinical ventricular tachycardia early in the stimulation protocol and obviating the need for left ventricular catheterization in most patients. These advantages are counterbalanced by an early near-maximal yield of nonclinical arrhythmias, including a 10% incidence of induced sustained polymorphic ventricular tachycardia requiring direct-current countershock.

On the other hand, the initial use of burst overdrive pacing and single and double extrastimuli in the right and left ventricles (protocol B) minimizes the yield of induced nonclinical arrhythmias, especially those that are polymorphic (4%), by obviating the need for triple extrastimuli in 61% of patients. However, triple extrastimuli will still be required to induce clinical ventricular tachycardia in 24% of patients, and it should be pointed out that the overall incidence of induced nonclinical ventricular tachycardia is similar with both protocol A and protocol B.

When a patient's spontaneous episodes of ventricular tachycardia are well documented, one may wish to use protocol A, since nonclinical arrhythmias that may be induced will be readily identifiable as such. However, in patients with suspected but undocumented ventricular tachycardia, e.g., patients with out-of-hospital cardiac arrest or unexplained syncope, it may be unclear whether induced ventricular tachycardia is a clinically significant arrhythmia, especially if the tachycardia is polymorphic and induced by triple extrastimuli. For these patients we recommend use of protocol B.

References

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