Determinants of induced sustained arrhythmias in survivors of out-of-hospital ventricular fibrillation

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ABSTRACT We prospectively studied 196 consecutive survivors of out-of-hospital ventricular fibrillation (VF) not associated with acute myocardial infarction and 46 consecutive, control patients without prior ventricular arrhythmias. Programmed stimulation included two extrastimuli (S1 protocol) in all patients and three extrastimuli (S4 protocol) in the last 140 study patients and in all control patients. Sustained ventricular tachycardia (VT) or VF was not induced in any control patient. In study patients, logistic regression identified two independent predictors of induced, sustained VT for both S3 and S4 protocols: prior spontaneous, sustained VT (37 patients; p ≤ .001) and prior myocardial infarction (113 patients; p = .005). With the S3 protocol, sustained VT was induced in 54% of patients with both prior myocardial infarction and prior sustained VT vs 4% without either; with the S4 protocol, sustained VT was induced in 91% vs 13%, respectively. Eighty-three percent of induced VT episodes had a cycle length less than 300 msec, and all required termination by cardioversion or pacing. VF was induced only in survivors of out-of-hospital VF without prior, spontaneous, sustained VT (S3 protocol, 9%; S4 protocol, 24%) but not in study patients with prior sustained VT (S3, p = .10; S4, p = .05) or control patients (S3, p = .06; S4, p = .01). The mean coupling intervals of extrastimuli that induced VF were not statistically different from the intervals that induced sustained VT. These data indicate that prospective analysis of clinical variables can identify survivors of out-of-hospital VF with a very high and very low probability of induced sustained VT and that there is a significant correlation between induced VF and spontaneous out-of-hospital VF as the only clinical arrhythmia.


PROGRAMMED VENTRICULAR STIMULATION was developed as a clinical tool in patients with recurrent sustained ventricular tachycardia (VT) and applied subsequently to survivors of cardiac arrest.3–10 It can reproduce the clinical arrhythmia in approximately 90% of patients with recurrent sustained VT,9–14 but in survivors of cardiac arrest the incidence of arrhythmia induction has been lower and the correlation between clinical and induced arrhythmias has been weaker. There are several possible reasons for this difference. First, in contrast to sustained VT, which is a specific arrhythmia, cardiac arrest is a clinical syndrome. The presenting arrhythmia is most frequently ventricular fibrillation (VF) but can be VT, a bradyarrhythmia, or an undocumented rhythm in 18% to 55% of patients.3–10 Second, in some patients, VT may be precipitated by transient electrophysiologic conditions that have resolved by the time of electrophysiologic study. Third, VT may be the initiating arrhythmia for some patients found in VF. An additional factor confounding the correlation between induced and clinical arrhythmias in survivors of VF is that VF can be a nonspecific outcome of programmed stimulation.14–16

Although VF is the arrhythmia most frequently recorded during out-of-hospital cardiac arrest, no previous study has focused on results of programmed stimulation in survivors of out-of-hospital VF. Use of results from previous, retrospective studies of survivors of cardiac arrest is hindered by variability in presenting arrhythmias, pacing protocols, and location of arrest (in-hospital vs out-of-hospital). An accurate estimate of the priori probability of inducing an arrhythmia in survivors of out-of-hospital VF could be used to identify those who would benefit most from electrophysiologic testing. We analyzed the determinants of induced arrhythmias, using a uniform pacing pro-
protocol, in prospectively studied, consecutive survivors of out-of-hospital VF.

Methods

Study patients. We prospectively evaluated 196 consecutive patients who met the following criteria: (1) All survived out-of-hospital VF not associated with acute myocardial infarction or rapid atrioventricular conduction of an atrial arrhythmia. (2) Electrophysiologic study induced a uniform, basic programmed stimulation protocol. (3) Spontaneous, sustained VT did not occur in the interval between VF and electrophysiologic study. The clinical characteristics of study patients are summarized in table 1. Patients were studied at the University of Washington (n = 115), Stanford University (n = 38), or the University of Oregon (n = 43). The characteristics of patients studied at each institution were similar.

Subgroups of study patients. Study patients were divided prospectively into two subgroups. The subgroup with prior sustained VT included 37 patients with a history of spontaneous, sustained, monomorphic VT not associated with acute myocardial infarction. The complementary subgroup with out-of-hospital VF only consisted of 158 patients who did not qualify for the other subgroup. Separate data analyses were performed for all patients and for the subgroup with out-of-hospital VF only because we hypothesized that survivors of out-of-hospital VF with prior sustained VT might be similar to patients with recurrent sustained VT.

At the time of out-of-hospital VF, more patients with prior sustained VT were receiving antiarrhythmic drugs than patients with out-of-hospital VF only (43% vs 20%; p = .007). Patients’ primary physicians selected these antiarrhythmic drugs empirically or assessed their efficacy by qualitative inspection of the frequency of asymptomatic ventricular arrhythmias during electrocardiographic monitoring for various durations. Antiarrhythmic drugs were not selected in any patient by rigorous, quantitative electrocardiographic monitoring or electropharmacologic testing. No patient had received nonpharmacologic antiarrhythmic therapy before out-of-hospital VF.

Control patients. The programmed stimulation protocol was validated in 46 consecutive, prospectively studied control patients who underwent electrophysiologic study for clinical indications other than syncope or documented or suspected ventricular arrhythmias. Patients were studied at Stanford University (n = 25) and the University of Oregon (n = 21). The clinical characteristics of control patients are summarized in table 2. In comparison with study patients, control patients were younger (p ≤ .001) and had a lower incidence of structural heart disease (p ≤ .001).

Electrophysiologic study protocol. All antiarrhythmic medications, except β-blockers required for treatment of angina (11 study patients) and digoxin (34 study patients), were discontinued for at least five half-lives. After written, informed consent was obtained, multipolar electrode catheters were positioned in the high right atrium, right ventricular apex, and His bundle position. Three to six surface electrocardiographic leads were recorded simultaneously with intracardiac electrograms. Stimuli were 2 msec rectangular pulses delivered at twice diastolic threshold.

In all patients, we followed a strict, basic stimulation protocol until either sustained VT or VF was initiated or the protocol was completed. First we performed incremental atrial pacing up to the rate at which atrioventricular node Wenckebach block occurred. The basic protocol included one extrastimulus (S₂) and two extrastimuli (S₃) from the right ventricular apex and outflow tract at basic pacing cycle lengths of 600 and 400 msec. In the last 140 study patients and in all control patients, the protocol included a third extrastimulus (S₄) from both right ventricular sites if the basic protocol did not induce a sustained ventricular tachyarrhythmia. In all study and control patients, the coupling interval of each extrastimulus was shortened until refractoriness occurred. Data were analyzed separately for the basic protocol (S₃ protocol) and for the entire protocol with S₄ (S₄ protocol).

Definitions of induced arrhythmias. No induced VT: Five or fewer repetitive ventricular responses. Nonsustained VT: Spontaneously terminating VT lasting six complexes to 30 sec. Sustained VT: VT lasting longer than 30 sec or requiring termination by cardioversion or pacing in less than 1 sec. Monomorphic VT: Uniform QRS morphology in each recorded ECG lead. Polymorphic VT: Continuously varying QRS morphology in any ECG lead. VF: Polymorphic sustained ventricular tachyarrhythmia with a mean cycle length less than 200 msec. The cycle length of induced sustained arrhythmias was measured after the first 10 right ventricular electrograms. This definition was not influenced by cycle-length variability in the first few complexes but identified induced VT that later degenerated to VF. When

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**TABLE 1**

Clinical characteristics of study patients (n = 196)

<table>
<thead>
<tr>
<th>Age (yr, mean ± SD)</th>
<th>58 ± 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>160 (82%)</td>
</tr>
<tr>
<td>Female</td>
<td>36 (18%)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>135 (69%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>113 (58%)</td>
</tr>
<tr>
<td>LV aneurysm</td>
<td>25 (13%)</td>
</tr>
<tr>
<td>Myocardial or valvular disease</td>
<td>52 (26%)</td>
</tr>
<tr>
<td>No structural heart disease</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>Arhythmia characteristics</td>
<td></td>
</tr>
<tr>
<td>Prior sustained monomorphic VT</td>
<td>38 (19%)</td>
</tr>
<tr>
<td>OHVF only</td>
<td>158 (81%)</td>
</tr>
<tr>
<td>Antiarrhythmic drug therapy at OHVF</td>
<td>49 (25%)</td>
</tr>
<tr>
<td>LV ejection fraction (mean ± SD)</td>
<td>0.40 ± 0.16^</td>
</tr>
</tbody>
</table>

^Values for 180 patients.

**TABLE 2**

Clinical characteristics of control patients (n = 46)

<table>
<thead>
<tr>
<th>Age (yr, mean ± SD)</th>
<th>41 ± 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32 (70%)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (30%)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Myocardial or valvular disease</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>No structural heart disease</td>
<td>37 (80%)</td>
</tr>
<tr>
<td>Indication for electrophysiologic study</td>
<td></td>
</tr>
<tr>
<td>Supraventricular tachyarrhythmia</td>
<td>29 (63%)</td>
</tr>
<tr>
<td>WPW on postoperative study</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Conduction system disease</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Minimal palpitations</td>
<td>6 (13%)</td>
</tr>
</tbody>
</table>

WPW = Wolff-Parkinson-White syndrome.
sustained VT was induced more than once, the cycle length of the first induced episode was reported.

**Variables analyzed.** We analyzed 13 variables describing clinical, catheterization, and arhythmia data. Clinical variables included age, sex, presence, and type of structural heart disease, prior myocardial infarction, infarct location, and NYHA heart failure class. Three variables related to characteristics of clinical arrhythmias: prior sustained VT, antiarrhythmic drug treatment at the time of out-of-hospital VF, and interval from out-of-hospital VF to electrophysiologic study. We analyzed this last variable as a measure of whether arrhythmias initiated by programmed stimulation have time-dependent electrophysiologic properties or depend only on a chronic electrophysiologic substrate. Catheterization and angiographic variables were left ventricular ejection fraction and left ventricular aneurysm. Myocardial infarction was diagnosed on the basis of either a history of characteristic evolutionary electrocardiographic and enzyme changes or pathologic Q waves in two or more electrocardiographic leads.

**Statistical analysis.** Basic comparative statistics were calculated with the chi-square test with Yates’ correction, analysis of variance, or Student’s t test. To estimate the magnitude of type II error present when statistically significant differences were not detected between the coupling intervals of extrastimuli that induced sustained monomorphic VT and VF, we calculated the probability that the mean coupling intervals differed by 25 msec.17

The independent clinical variables were evaluated by univariate statistical techniques for their strength of association with two dependent variables, induced sustained monomorphic VT and induced VF. Separate analyses were performed for all patients and for the prospectively chosen subgroup with out-of-hospital VF only. When missing values variables occurred, univariate analysis was restricted to those patients for whom values were defined.

Stepwise logistic regression analysis was then applied to variables that had univariate predictive value (p < .05); this analysis was used to identify variables with significant independent predictive value (p < .05). Only one variable with missing values (left ventricular ejection fraction, n = 180) was a univariate predictor. Because of the known importance of left ventricular ejection fraction in many aspects of cardiac disease, its effects were analyzed in two ways. First, we performed multivariate analysis restricted to the subset of patients for whom it was determined; second, we substituted the median value for the missing values and applied the analysis to all patients.9, 18

These two analyses gave similar results.

**Results**

**Induced arrhythmias: study group.** Overall, sustained monomorphic VT was induced in 21% of patients by the S3 protocol vs 40% by the S4 protocol (p < .001). VF was induced in 8% by the S3 protocol vs 19% by the S4 protocol (p = .004). Sustained polymorphic VT was not induced in any patient. Both sustained monomorphic VT and VF were induced in one patient by the S4 protocol. Complete data are shown in table 3. The incidence and types of induced arrhythmias were similar at the three institutions.

The cycle length of induced sustained VT was 250 msec or less in 45% of episodes, 250 to 300 msec in 38%, 300 to 350 msec in 12%, and over 350 msec in 5%. All episodes of induced sustained VT required cessation: immediate cardioversion in 32%, overdrive or burst pacing in 58%, and secondary cardioversion after pacing accelerated VT in 10%.

**Predictors of induced, sustained monomorphic VT.** Table 4 shows univariate correlates of induced sustained VT for all patients and for patients with out-of-hospital VF only. Results for the S3 and S4 protocols are similar. Three variables measure coronary artery disease or its complications: presence of coronary artery disease, myocardial infarction, and left ventricular aneurysm. Two variables measure left ventricular function: left-ventricular ejection fraction and NYHA functional class. Two variables describe clinical arrhythmias: prior sustained VT and history of antiarrhythmic drug therapy at the time of out-of-hospital VF. This last variable correlated strongly with prior sustained VT and was not significant when the analysis was restricted to patients with out-of-hospital VF only.

Logistic regression identified only two variables as independent predictors of induced sustained VT: prior myocardial infarction (S3 protocol, p = .001; S4 protocol, p = .005) and prior sustained VT (S3 protocol, p = .001; S4 protocol, p = .0004). When the analysis was restricted to patients with out-of-hospital VF only, the only independent predictor was prior myocardial infarction (S3 protocol, p = .003; S4 protocol, p = .005). Figure 1 shows the incidence of induced, sustained VT stratified by these two variables. For the S3 protocol, the incidence of induced sustained VT was 54% for patients with both predictors, 31% for patients with one predictor, and 4% for patients without either predictor; for the S4 protocol, the incidence of induced sustained VT was 91%, 54%, and 13%, respectively.

**Predictors of induced VF.** The only variable analyzed that correlated with induced VF was absence of prior sustained VT. The S3 protocol induced VF in 15 of 158 patients with out-of-hospital VF only (9%) vs none of 38 (0%) with prior sustained VT (p = .10); the S4 protocol induced VF in 27 of 112 patients with out-of-hospital VF only (24%) vs none of 28 (0%) with prior sustained VT (p = .01).
Induced arrhythmias: control group. Sustained VT or VF was not induced in any control patient. The incidence of induced VF was higher for patients with out-of-hospital VF only than for control patients (S₁ protocol, p = .01; S₄ protocol, p < .0001). Non-sustained VT was not induced in any control patient.

Coupling intervals of extrastimuli that induced VT and VF. Table 5 shows the mean coupling intervals of extrastimuli that induced sustained VT and VF in study patients as well as the shortest coupling intervals of extrastimuli that captured the ventricle in control patients. There is a trend for shorter coupling intervals with increasing numbers of extrastimuli in each patient group (sustained VT, p < .001; VF, p = .05; control, p < .001). For each extrastimulus, the mean coupling interval associated with induction of VF was shorter than the mean interval associated with induction of sustained VT, but these differences were not significant (p > .20). The probability of missing a 25 msec difference between the mean coupling intervals of extrastimuli that induced VF and sustained VT was .04 for the S₃ protocol and .03 for the S₄ protocol. The fraction of very short coupling intervals (≤ 180 msec) also was not statistically different. The shortest coupling interval required for induction of arrhythmia was 170 msec in three patients (VF in two and sustained VT in one). The shortest S₃ and S₄ coupling intervals that captured the ventricle in control patients were significantly shorter than those required for induction of VF in study patients (p < .03).

Time from VF to electrophysiologic study. Figure 2 shows the incidence of induced arrhythmias as a function of time between out-of-hospital VF and electrophysiologic study in patients with out-of-hospital VF only. Neither induced sustained VT nor induced VF correlated with time from VF to study for either the S₁ or S₄ protocol. Results for the entire study group were similar.

Discussion

Our study differs from previous studies of programmed stimulation in survivors of cardiac arrest in several ways. First, the patient population is limited to survivors of out-of-hospital VF; patients with in-hospital VF and those in whom the arrest rhythm was not documented to be VF were excluded. Second, we included only consecutive, prospectively studied patients. Third, we analyzed results only for uniform pacing protocols.

The principal new positive findings of this study about survivors of out-of-hospital VF are that prior myocardial infarction and prior spontaneous, sustained monomorphic VT are strong, independent predictors of induced sustained monomorphic VT and that the only predictor of induced VF is absence of prior, sustained monomorphic VT. These results apply for both S₃ and S₄ pacing protocols. The principal new negative finding is that the incidence of induced VT or VF does not depend on the time from out-of-hospital VF to electrophysiologic study. Our study also confirms for survivors of out-of-hospital VF a result which has been reported for other groups of patients: use of a third extrastimulus increases the incidence of both induced sustained VT and VF.

Induced arrhythmias: comparison with previous studies. Three previous retrospective studies of survivors of cardiac arrest report results of programmed stimulation for subgroups in whom the clinical arrhythmia was VF. Two studies included patients with in-hospital VF, and one study does not specify the patients' locations at the time of VF. The pacing protocol included S₃ and rapid ventricular pacing in each study; the fraction of patients tested with S₄ varied from 11% to 90%, and two studies used left ventricular pacing and isoproterenol in a minority of patients. In these studies, the incidence of induced sustained VT varied from 23% to 41% and the incidence of induced...
VF from 11% to 22%. The results of our study are in a similar range for induced sustained VT (S₃ protocol, 21%; S₄ protocol, 40%) and induced VF (S₃ protocol, 8%; S₄ protocol, 19%).

**Time from out-of-hospital VF to electrophysiologic study.** One possible explanation for the relative low incidence of induced, sustained arrhythmias in survivors of out-of-hospital VF is that some episodes of out-of-hospital

\[
\begin{array}{ccc}
\text{S₃ Protocol (n=196)} & & \\
\text{Prior VT} & & \\
+ & + & + \\
54\% (26) & 24\% (86) & 31\% (112) \\
+ & - & + \\
25\% (12) & 4\% (72) & 7\% (84) \\
- & + & - \\
45\% (38) & 15\% (158) & \\
- & - & - \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{S₄ Protocol (n=140)} & & \\
\text{Prior VT} & & \\
+ & + & + \\
91\% (22) & 40\% (65) & 53\% (87) \\
+ & - & + \\
67\% (67) & 13\% (47) & 19\% (53) \\
- & + & - \\
86\% (28) & 29\% (112) & \\
- & - & - \\
\end{array}
\]

**FIGURE 1.** Incidence of induced sustained, monomorphic VT in survivors of out-of-hospital VF stratified by history of spontaneous sustained, monomorphic VT (prior VT) and history of myocardial infarction (MI). Top. Data for all 196 patients, with a maximum of two extrastimuli from two right ventricular sites (S₃ protocol). Bottom. Results for the last 140 patients in whom the protocol included a third right ventricular extrastimulus from two right ventricular sites (S₄ protocol). + = condition present; - = condition absent. Numbers shown as percent indicate the incidence of induced sustained VT in each patient subgroup. Numbers in parentheses are the number of patients in each subgroup.

**TABLE 5**

<table>
<thead>
<tr>
<th>Coupling intervals</th>
<th>S₁S₂</th>
<th>S₂S₃</th>
<th>S₃S₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained VT induced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>7</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Coupling interval</td>
<td>301 ± 63</td>
<td>229 ± 40</td>
<td>211 ± 33</td>
</tr>
<tr>
<td>Coupling interval=180 msec</td>
<td>0 (0%)</td>
<td>3 (10%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>VF induced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>2</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Coupling interval</td>
<td>225</td>
<td>216 ± 25</td>
<td>198 ± 22</td>
</tr>
<tr>
<td>Coupling interval=180 msec</td>
<td>0 (0%)</td>
<td>2 (15%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Control patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>46</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Shortest interval</td>
<td>228 ± 25</td>
<td>188 ± 27</td>
<td>179 ± 30</td>
</tr>
</tbody>
</table>

*For study patients, the coupling interval of the last extrastimulus that induced sustained VT or VF is shown. For control patients, the shortest coupling interval that resulted in ventricular capture for each extrastimulus is shown.

VF are precipitated by transient arrhythmogenic conditions. Such conditions may either be applied to a normal electrophysiologic substrate or superimposed on a necessary, but insufficient, chronic arrhythmogenic substrate. If this were the case, the incidence of arrhythmia induction might be higher for patients studied early after out-of-hospital VF. We found no such correlation, possibly because transient precipitating factors may have resolved too rapidly to be detected in this study. Possible transient arrhythmogenic conditions with such a time course might include ischemia, metabolic abnormalities, or changes in the autonomic
nervous system. The practical implication of this finding is that the yield of induced sustained VT or VF does not depend on the delay to study up to 1 month, and possibly up to 6 months.

**Predictors of induced arrhythmias.** One previous study analyzed predictors of arrhythmia induction in patients with a variety of ventricular tachyarrhythmias using primarily two extrastimuli. Independent predictors of induced VT (≥ 5 complexes) in that study were clinical sustained VT (vs clinical nonsustained VT or VF), prior myocardial infarction, and male sex. Because the clinical significance of induced ventricular arrhythmias may depend on arrhythmia type, we performed separate analyses for each type of induced, sustained arrhythmia. We found that two of the variables identified by Schoenfeld et al., prior sustained VT and prior myocardial infarction, were independent predictors of induced sustained VT in survivors of out-of-hospital VF using either S3 or S4 protocols. In patients with both predictors, the incidence of induced, sustained VT was comparable to that reported for postinfarction survivors with recurrent, sustained VT. In contrast to our findings on predictors of induced sustained VT, we found that the only predictor of induced VF was absence of prior sustained VT.

**Significance of induced VT.** Most studies of the onset of spontaneous VF in humans have found the initiating arrhythmia to be sustained monomorphic VT in 60% to 87% of patients and polymorphic VT that degenerates to VF within a few complexes in 13% to 40%. The arrhythmia induced most frequently in survivors of VF in the present and previous studies was sustained VT. Our finding that prior sustained VT is a strong, independent predictor of induced sustained VT supports the hypothesis that programmed stimulation can identify survivors of out-of-hospital VF in whom the initiating arrhythmia is sustained VT. The observation that most episodes of induced VT had a short cycle length and caused rapid hemodynamic collapse is consistent with this hypothesis. Stevenson et al. also reported short cycle lengths and hemodynamic instability for VT induced in survivors of cardiac arrest.

In our patients with prior sustained VT, antiarrhythmic therapy at the time of out-of-hospital VF was absent or inadequate by current standards. We therefore believe that our findings should not be applied to patients in whom antiarrhythmic therapy at the time of out-of-hospital VF has been judged effective by techniques with documented predictive accuracy.

The second strong independent predictor of induced, sustained monomorphic VT was prior myocardial infarction. One explanation for this correlation is that the VF is frequently initiated by sustained VT in postinfarction patients. However, programmed stimulation induces sustained, monomorphic VT of uncertain clinical significance in 11% to 16% of postinfarction patients. In some of our patients, the postinfarction substrates for VT might not be the cause of VF. 

**Significance of induced VF.** It is difficult to evaluate the significance of induced VF in survivors of VF. Although initial studies reported a high correlation between induced and spontaneous VF, subsequent studies found that induced VF may be nonspecific. For comparison, the clinical significance of induced sustained VT in patients with spontaneous, sustained VT was validated by two methods: comparison of induced and clinical VT morphologies and retrospective analysis of arrhythmia recurrence in patients in whom therapy was evaluated by programmed stimulation. In survivors of out-of-hospital VF, the first approach cannot be used. The second will require a very large cohort of patients for meaningful analysis because of the low incidence of induced VF in survivors of out-of-hospital VF.

Our data show a significant correlation between induced VF and spontaneous out-of-hospital VF as the only clinical arrhythmia. The incidence of induced VF was higher in patients with out-of-hospital VF only than in patients with prior sustained VT or in a concurrent control group. These differences could not be attributed specifically to achievement of shorter coupling intervals in patients with induced VF. This last finding contrasts with a previous report that induction of nonspecific VT or VF is strongly associated with use of short coupling intervals.

Results of several retrospective studies support the correlation we identified prospectively between clinical and induced VF. The highest incidence of induced VF in previous studies has been in survivors of VF and has varied from 11% to 22%. In contrast, the incidence of induced, nonspecific VF has been low with pacing protocols similar to ours. Three large studies analyzed the incidence of induced nonspecific VF with S3 protocols at 2 to 4 times threshold in patients without ventricular arrhythmias. Excluding patients with hypertrophic cardiomyopathy who may be particularly vulnerable to induced nonspecific VF, VF was induced in only five of 232 patients (2%). A limitation of each of these studies, which also applies to ours, is that the clinical characteristics of control patients and survivors of VF differ. The incidence of induced VF in most studies of patients with myocardial infarction or cardiomyopathy without ventricular arrhythmias cannot be compared meaningfully to our findings.
because they limited pacing to two extrastimuli and/or used induced nonsustained VT as an end point. In the only study of postinfarction patients in whom an S₄ protocol was continued to ventricular refractoriness, the incidence of induced VF was 3%.²⁴

Implications for electropharmacologic testing. The utility of electropharmacologic testing in any group of patients depends on the product of the probability of inducing a suitable arrhythmia and the probability of accurately predicting a drug that will be effective once the arrhythmia has been induced. Electropharmacologic testing has been validated most thoroughly in patients with induced, sustained monomorphic VT.² 28–31 In addition, the likelihood of requiring multiple cardioversions during serial electropharmacologic testing, with the accompanying discomfort, psychological stress, and risk, is lower in patients with induced VT than in those with induced VF. Our findings indicate that programmed stimulation is most likely to induce sustained VT in survivors of out-of-hospital VF with a history of either myocardial infarction or sustained VT. Based on currently available data, these patients are the best candidates for electropharmacologic testing.

In the third of our patients who had neither a history of myocardial infarction nor sustained VT, the incidence of induced sustained VT was very low (S₃ protocol, 4%; S₄ protocol, 13%). Since electropharmacologic testing predicts an antiarhythmic drug effective in 53% to 70% of patients with induced sustained VT using an S₃ protocol¹, 9, 30, 3¹ and in 30% to 38% with an S₄ protocol, 3⁰, 3² the expected incidence of predicted drug efficacy in this patient subgroup is 2% to 5% for either S₃ or S₄ protocols.

In these patients, the clinical utility of programmed stimulation depends on two unresolved questions: (1) Is there a study outcome that predicts a sufficiently low risk of recurrent VF to justify withholding specific antiarrhythmic therapy? (2) What is the predictive accuracy of electropharmacologic testing with only nonsustained VT or VF as end points in this patient population? Reported data are inadequate to answer either questions definitively.

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Vol. 76, No. 5, November 1987 1059
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Circulation. 1987;76:1053-1060
doi: 10.1161/01.CIR.76.5.1053

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