Prognostic significance of the number of induced ventricular complexes during assessment of therapy for ventricular tachyarrhythmias

CHARLES D. SWERDLOW, M.D., ROGER A. WINKLE, M.D., AND JAY W. MASON, M.D.

ABSTRACT We analyzed 255 long-term trials of antiarrhythmic therapy, each of which had been evaluated at electrophysiologic study, to identify the maximum number of induced ventricular complexes consistent with the long-term efficacy of antiarrhythmic therapy. All patients had spontaneous and inducible sustained ventricular tachycardia or ventricular fibrillation. The incidence of therapeutic efficacy at 1 month and throughout follow-up was similar for trials in which zero, one, two, three, four, five, six to 10, and 11 to 15 complexes were induced, but significantly lower (p < .001) for trials in which 16 or more complexes were induced. The cumulative incidence of efficacy at 1 year was 75 ± 5% for 0 to 5 induced complexes, 72 ± 11% for six to 10 complexes, 83 ± 15% for 11 to 15 complexes, 42 ± 10% for 16 complexes to 15 sec, and 48 ± 6% for sustained ventricular tachycardia. At 1 year, the incidence of "sudden death–free" survival was higher for patients in trials that prevented initiation of sustained ventricular tachycardia than for those in trials that permitted initiation of sustained ventricular tachycardia (91 ± 3% vs 75 ± 6%; p = .01). The duration of the arrhythmia induced at therapy assessment was in the range of 11 to 20 complexes for only 4% of trials. Antiarrhythmic therapy is likely to be effective if as many as 15 complexes are induced at therapy assessment. The best cutoff, between 11 and 20 complexes, is difficult to identify because of the small fraction of trials in this range. Patients in whom initiation of sustained ventricular tachycardia is not prevented are at high risk for arrhythmia recurrence and sudden death. Circulation 68, No. 2, 400–405, 1983.

ASSESSMENT of antiarrhythmic therapy at electrophysiologic study has been reported to predict its long-term efficacy or inefficacy in patients with ventricular tachyarrhythmias. However, the maximum number of induced ventricular complexes considered to be consistent with effective long-term therapy has varied among investigators and has not been stated explicitly in some studies. No study has reported criteria proven to most accurately predict prophylaxis against the clinical arrhythmia. We therefore sought to determine the specific number of induced complexes that would be the best cutoff for predicting efficacy of a tested therapy in our laboratory.

Methods

Patients. We analyzed 255 long-term trials of antiarrhythmic therapy that had been evaluated at electrophysiologic study in 178 patients with spontaneous sustained ventricular tachycardia or ventricular fibrillation not associated with acute myocardial infarction. In all patients sustained ventricular tachycardia lasting longer than 15 sec was induced by programmed stimulation. The patients' clinical characteristics are summarized in table 1.

Electrophysiologic study protocol. All antiarrhythmic medications except digoxin were discontinued at least 24 hr before initial electrophysiologic study.

Multipolar electrode catheters were placed in the high right atrium, right ventricular apex, and His bundle recording position. Three to six surface electrocardiographic leads were recorded simultaneously with intracardiac electrograms. A W. P. Instruments stimulator and stimulus isolator were used for programmed stimulation. Stimuli were rectangular pulses with a duration of 2 msec and a current strength twice the diastolic capture threshold. A strict programmed stimulation protocol was followed. In all patients, it included atrial pacing up to the rate at which atrioventricular node Wenckebach block occurred, up to two right ventricular extrastimuli in sinus and ventricular paced rhythms at multiple basic pacing cycle lengths, bursts of rapid ventricular pacing to a minimum cycle length of 200 msec, and when necessary, the use of a second right ventricular site and isoproterenol infusion. In trials 21 through 255, a third right ventricular extrastimulus was used for baseline arrhythmia induction if a sustained arrhythmia could not be induced with only two extrastimuli. In nine patients in whom ventricular tachycardia could not be induced by stimulation in the right ventricle, the pacing protocol was repeated in the left ventricle.
TABLE 1
Clinical characteristics of 178 patients with ventricular tachyarhythmias

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (yr)</th>
<th>56±13</th>
<th>Male:female ratio</th>
<th>6:1:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac diseaseA</td>
<td>Coronary artery disease</td>
<td>133 (75)</td>
<td>Previous myocardial infarction</td>
<td>126 (71)</td>
</tr>
<tr>
<td></td>
<td>Left ventricular aneurysm</td>
<td>71 (40)</td>
<td>Myocardial disease</td>
<td>13 (7)</td>
</tr>
<tr>
<td></td>
<td>Valvular disease</td>
<td>16 (9)</td>
<td>No structural heart disease</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Arrhythmia characteristics</td>
<td>Sustained ventricular tachycardia</td>
<td>169 (93)</td>
<td>Ventricular fibrillation</td>
<td>9 (7)</td>
</tr>
<tr>
<td></td>
<td>Cardioversion required</td>
<td>137 (77)</td>
<td>Cardiac arrest</td>
<td>57 (32)</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td>LVEDP (mm Hg)</td>
<td>17±9 (n = 151)</td>
<td>Cardiac index (l/min/m²)</td>
<td>2.4±0.7 (n = 126)</td>
</tr>
<tr>
<td></td>
<td>Left ventricular ejection fraction</td>
<td>36±14 (n = 128)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>I</td>
<td>37 (21)</td>
<td>II</td>
<td>80 (45)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>54 (30)</td>
<td>IV</td>
<td>7 (4)</td>
</tr>
</tbody>
</table>

LVEDP = left ventricular end-diastolic pressure; NYHA = New York Heart Association.

*Coronary artery disease: the diameter of at least one major coronary artery was narrowed by ≥ 70% or a myocardial infarction had occurred. Myocardial disease: ventricular hypertrophy or dilatation documented by echocardiography or contrast angiography in the absence of coronary artery disease or valvular heart disease; presence of hypertrophy or fibrosis on endomyocardial biopsy was used as confirmatory evidence. Valvular heart disease: hemodynamically significant stenosis or insufficiency of one or more cardiac valves, both auscultatory and echocardiographic findings of mitral valve prolapse, or previous valve surgery. Absence of structural heart disease: normal physical examination, resting ECG, chest x-ray, two-dimensional ECG, exercise treadmill test, and endomyocardial biopsy; whenever this diagnosis was in question, complete hemodynamic and angiographic evaluation, including contrast left and right ventriculograms and coronary arteriography, was performed.

*Numbers in parentheses are percents.

During follow-up electrophysiologic studies, a single quadripolar catheter was used for pacing and recording. Trials of drugs administered orally were assessed only after the drug and its active metabolites had reached steady-state levels. Lorcaine was assessed after 1 week of therapy. Amiodarone was assessed (37 trials in 35 patients) after 2 weeks to 1 month. Postoperative electrophysiologic studies were conducted 10 to 14 days after patients underwent surgery guided by electrical activation sequence mapping.

Antiarrhythmic drugs were administered according to a previously described protocol.1 Drug efficacy was assessed by the pacing protocol described above, with use of the pacing site in which arrhythmia induction had succeeded in the control state. In patients who required isoproterenol for arrhythmia induction, isoproterenol was administered at the same dose during therapy assessment. In all patients the complete pacing protocol (multiple extrastimuli delivered at four basic pacing cycle lengths) was used during therapy assessment until a sustained ventricular tacharyrhythmia was induced or until the entire protocol was completed, including up to two extrastimuli in trials 1 to 20 and three extrastimuli in trials 21 through 255. Thus the pacing protocol for drug assessment was more exhaustive than the control protocol whenever a submaximal pacing program successfully induced sustained ventricular tachycardia or fibrillation before but not during therapy assessment. For example, even if ventricular tachycardia was induced by a single extrastimulus during ventricular drive at a cycle length of 500 msec in the control state, during therapy assessment the entire protocol, including up to three extrastimuli (in the last 235 patients) delivered at all four drive cycle lengths of 600, 500, 430, and 400 msec, would have been used before a drug efficacy prediction was made.

Antiarrhythmic therapy. A total of 173 long-term trials of antiarrhythmic drugs alone, 48 trials of surgery guided by electrical activation sequence mapping, and 34 trials of drugs in patients who had previously undergone mapping-directed surgery were assessed at electrophysiologic study. Among the 173 drug trials, long-term drug therapy was instituted on the basis of induction of less than six ventricular complexes during therapy assessment in 54 trials; therapy was also instituted on the basis of the most markedly reduced rate or duration of induced tachycardia or an increased number of extrastimuli required for induction in 119 trials. Among the 82 trials of surgery or drugs combined with previous surgery, fewer than six ventricular complexes were induced in 48 cases (surgery alone, 38; surgery and drug, 10), and therapy was based on reduction of tachycardia rate, duration, or ease of induction in the other 34 trials (surgery alone, 10; surgery and drug, 24). (For the purposes of therapy selection, we considered an increase in the number of required extrastimuli, but not a simple increase in the effective drive rate, as a decrease in the ease of arrhythmia induction; this criterion could not be met, of course, in patients who required three extrastimuli for arrhythmia induction in the baseline study.) Drug doses for long-term oral therapy were adjusted to achieve drug plasma concentrations equal to or greater than those present during therapy assessment studies.

Drugs were discontinued because of arrhythmia recurrence, intolerable toxicity, or noncompliance by the patient. Arrhythmia recurrence was defined as spontaneous ventricular tachycardia of greater than 10 beats in duration.

Cardiac surgery guided by intraoperative electrical activation sequence mapping was performed in 64 selected patients for whom no drug prevented induction of sustained ventricular tachycardia.

Follow-up. The mean duration of follow-up was 7.8 months per trial (median 4 months, range 1 day to 64 months). Follow-up began on the date of therapy assessment and ended on the date of discontinuation of drug therapy due to intolerable toxicity, arrhythmia recurrence, study closure, loss to follow-up (one patient at 39 months), or sudden death. All patients underwent a minimum of 72 hr of ambulatory electrocardiographic monitoring during the first year of follow-up. Death was considered sudden if it occurred abruptly and was not preceded by primary circulatory collapse.11

Statistical analysis. Continuous data are presented as mean ± SD or as median and range. Basic comparative statistics were calculated with the chi-squared test with Yate's correction, Fisher's exact test, or the two-tailed t test for independent means. The cumulative incidences of arrhythmia recurrence and sudden death as functions of the number of ventricular complexes induced at therapy assessment were calculated by the method of Cutler and Ederer.12 Standard errors of cumulative propor-
tions were compared by the method of Greenwood.\textsuperscript{13} To estimate the magnitude of type II error present when statistically significant differences were not detected, we calculated the probability of missing a difference in efficacy equal to 25\% of the efficacy rate of trials in which the lowest number of complexes were induced.\textsuperscript{14} We constructed a relative operating characteristic graph\textsuperscript{15} to help identify the best cutoff point for predicting efficacy of tested therapy.

When both an intravenous and an oral trial of an antiarrhythmic drug had been performed, only results of the oral trial were analyzed. The incidences of arrhythmia recurrence and sudden death for patients treated with amiodarone were analyzed separately because of reports that results of electrophysio-

logic study may not accurately predict the long-term efficacy of this drug.\textsuperscript{16-18}

Results

Antiarrhythmic efficacy. Figure 1, A, and table 2 show the cumulative incidence of antiarrhythmic efficacy as a function of the number of ventricular complexes induced during therapy evaluation. Of the 75 episodes of arrhythmia recurrence, six (8\%) were 11 to 20 complexes in duration, five (7\%) were 21 complexes to 15

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Actuarial curves for long-term antiarrhythmic efficacy (A), survival (B), and antiarrhythmic efficacy based only on sustained arrhythmia recurrence (C) are stratified by the duration of the arrhythmia induced during therapy evaluation. Standard errors of the cumulative percentages are shown. Dashed lines, extensions of the curves beyond the last event to the longest duration of follow-up. In A, the curves for zero to five, six to 10, and 11 to 15 induced complexes are not statistically different. At 1 month the incidence of efficacy was significantly higher for trials in which 15 or fewer complexes were induced than for trials in which 16 or more complexes were induced (p < .001). This difference persisted throughout follow-up. In B, there is no significant difference in the incidence of sudden death among patients in trials in which zero to five, six to 10, 11 to 15 complexes, and 16 complexes to 15 sec of ventricular tachycardia were induced. At 1 year a significant difference in the incidence of sudden death is present between trials that prevented and those that permitted initiation of sustained ventricular tachycardia (p = .01). The data in C differ from those in A only in the first (zero to five complexes) and the fourth (16 complexes to 15 sec) groups. The statistical assessment of significance is the same as in A.}
\end{figure}
TABLE 2
Cumulative percent of effective trials at 1 year

<table>
<thead>
<tr>
<th>No. of induced complexes</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6–10</th>
<th>11–15</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of trials*</td>
<td>26</td>
<td>16</td>
<td>23</td>
<td>13</td>
<td>8</td>
<td>11</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Cumulative percent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effective*</td>
<td>84±9</td>
<td>61±14</td>
<td>68±14</td>
<td>74±17</td>
<td>100±0</td>
<td>90±9</td>
<td>72±11</td>
<td>80±18</td>
</tr>
</tbody>
</table>

*Number of long-term trials of antiarrhythmic therapy.

sec in duration, and 64 (85%) were sustained. There were no statistically significant differences in the incidence of antiarrhythmic efficacy among trials during which zero, one, two, three, four, five, six to 10, and 11 to 15 complexes were induced. In contrast, at 1 month the incidence of efficacy was significantly higher (p < .001) for therapy during which 15 or fewer complexes were induced than for those during which 16 or more complexes were induced, and this difference persisted throughout follow-up. The cumulative incidence of efficacy at 1 year, as a function of the duration of the induced arrhythmia, was 75 ± 5% for zero to five complexes, 72 ± 11% for six to 10 complexes, 83 ± 15% for 11 to 15 complexes, 42 ± 10% for 16 complexes to 15 sec, and 48 ± 6% for sustained ventricular tachycardia. In figure 1, C, a similar analysis was done, but asymptomatic, unsustained tachyarrhythmias were not considered failure of therapy. Since there were only 11 such cases, all of which occurred in the first month of therapy and only in the groups with zero to five induced complexes and 16 complexes to 15 sec of induced arrhythmia, the results in figure 1, C, are only slightly different from those in figure 1, A, and the same significant differences between groups persist.

The difference in cumulative incidence of efficacy between trials of therapy based on 15 or fewer and 16 or more induced complexes was greater if trials with amiodarone were excluded: 73 ± 5% vs 37 ± 6% at 12 months (p < .0001).

For trials in which six to 10 complexes were induced, the probability of missing a difference in cumulative efficacy at 1 year equal to 25% of the efficacy rate for trials in which zero to five complexes were induced was 7.6%. For trials in which 11 to 15 complexes were induced, this probability was 4.1%.

Figure 2 is a relative operating characteristic graph for the incidence of therapeutic efficacy at 1 month; the conditional probability of a true positive outcome (ordinate) and the conditional probability of a false positive outcome (abscissa) are displayed for different criteria used to predict efficacy. The ratio of true positive to false positive outcomes is higher if amiodarone trials are excluded. An inflection point occurs in both curves at 11 to 15 induced complexes. This indicates that cutoff points set at five, 10, or 15 complexes will result in similar ratios of true positive to false positive outcomes, whereas cutoff points set at 20 complexes or 15 sec results in lower ratios of true positive to false positive outcomes. Thus a cutoff at 15 complexes will classify correctly the most true positive outcomes consistent with maintaining a high true positive to false positive ratio.

FIGURE 2. Relative operating characteristic curve for the incidence of therapeutic efficacy at 1 month. The conditional probabilities of a true positive outcome (ordinate) and false positive outcome (abscissa) are displayed for different criteria used to predict efficacy. Separate curves for all trials and for trials excluding amiodarone are shown. The inflection point in both curves at 11 to 15 induced complexes indicates that cutoff points set at five, 10, or 15 complexes will result in similar ratios of true positive to false positive outcomes, whereas cutoff points set at 20 complexes or 15 sec will result in lower ratios of true positive to false positive outcomes. Based on these data the most liberal cutoff that still retains predictive accuracy is 15 induced complexes.
The number of long-term trials is displayed as a function of the duration of induced arrhythmias during therapy assessment in figure 3. Because only 4% of trials are in the range of 11 to 20 complexes, we cannot identify with certainty a specific number of complexes as the best cutoff. However any cutoff in this range will predict the same outcome for 96% of trials.

Sudden death. Figure 1, B, shows the cumulative incidence of "sudden death-free" survival as a function of the number of induced complexes during evaluation of therapy. At 1 year the incidence of sudden death-free survival was 92 ± 4% for zero to five induced complexes, 85 ± 10% for six to 10 complexes, 100% for 11 to 15 complexes, and 88 ± 11% for 16 complexes to 15 sec (NS). A significant difference in the incidence of sudden death-free survival between trials of therapies that prevented and those that permitted initiation of sustained ventricular tachycardia was present at 1 year (91 ± 3% vs 75 ± 6%; p = .01) and persisted throughout follow-up. When trials with amiodarone were excluded, the 12 month incidence of sudden death-free survival for sustained ventricular tachycardia trials was 66 ± 8%.

Discussion

We analyzed arrhythmia recurrence rates as a function of the number of complexes induced during therapy assessment to identify the maximum number of induced complexes consistent with long-term antiarrhythmic efficacy.

In previous reports, the criteria used to predict efficacy of a tested therapy have varied1-3 or have not been stated explicitly.4-9 Horowitz et al.2 evaluated arrhythmia recurrence in 20 patients who had spontaneous and inducible sustained ventricular tachycardia. In follow-up of 3 to 27 months, ventricular tachycardia did not recur in nine patients in whom no complexes were induced at drug assessment or in four patients in whom fewer than 10 complexes were induced. In contrast, all seven patients in whom sustained ventricular tachycardia was induced at drug assessment had arrhythmia recurrence within 1 to 22 days. Denes et al.3 reported results of therapy based on drug trials at electrophysiologic study in nine patients who had spontaneous and inducible sustained ventricular tachycardia. During follow-up of 3 to 44 months, ventricular tachycardia recurred in one of four patients in whom two or fewer complexes were induced on therapy, one of two patients in whom unsustained ventricular tachycardia (3 beats to 30 sec) was induced, and all three patients in whom sustained ventricular tachycardia was induced. In a previous report from our laboratory,10 the criterion used for predicting long-term drug efficacy was five or fewer complexes in patients who had inducible sustained ventricular tachycardia and two or fewer complexes in patients who had inducible unsustained ventricular tachycardia (6 beats to 15 sec). At 1 year, the cumulative incidence of arrhythmia recurrence was 20 ± 12% in trials predicted to be effective and 80 ± 23% in trials predicted to be ineffective.

The specific criterion used to predict antiarrhythmic drug efficacy was not stated in three additional reports which concluded that results of drug assessment at electrophysiologic study predict arrhythmia recurrence in patients with ventricular tachycardia4-6 and in two studies which report that results of electrophysiologic study predict arrhythmia-related mortality in survivors of out-of-hospital cardiac arrest.7-9

In this study, therapy infrequently prevented induction of all ventricular complexes; the incidence of subsequent arrhythmia recurrence was low regardless of the specific number of induced complexes, up to 15. However, patients in whom 16 or more complexes were induced during therapy were at greater risk for arrhythmia recurrence, and those in whom sustained ventricular tachycardia was induced were at greater risk for sudden death than patients in whom 15 or fewer complexes were induced.

This study has several limitations: (1) We could not analyze arrhythmia recurrence individually for each number of induced beats between six and 15 because of the small numbers of such trials. Our data are inadequate to identify a specific number of induced complexes between 11 and 20 that might represent the best cutoff point. However, because only 4% of trials fall in this range, any cutoff chosen between 11 and 20 complexes would have similar predictive power in our sub-
jects. (2) Long-term trials of therapies that did not prevent induction of sustained ventricular tachycardia included only drugs that reduced the rate of the induced tachycardia or increased the pacing stress required for induction. If this selection bias had not been present, the incidence of arrhythmia recurrence and sudden death might have been higher in this group. (3) Our results apply specifically to the pacing protocol we used, which differs in some respects from those used in other electrophysiology laboratories. (4) Electrophysiology study may not predict long-term inefficacy of certain drugs with accuracy. Our data are in agreement with the results of previous reports showing that initiation of sustained ventricular tachycardia is not an accurate predictor of long-term amiodarone inefficacy. (5) To achieve patient groups of sufficient size to perform meaningful actuarial analysis, we pooled data from patients who had heterogenous clinical characteristics and who received different therapies. Our results might not apply equally to all subgroups. Meaningful subgroup analysis would require a much larger patient population.

Ideally, criteria used to predict antiarrhythmic efficacy would detect all patients at risk for arrhythmia recurrence and recognize all patients with clinically relevant degrees of arrhythmia prophylaxis. These criteria might include data in addition to the number of induced complexes, such as drug-induced changes in the width of the tachycardia zone, the pacing stress required for tachycardia initiation, and the rate and morphology of the induced rhythm. Our data are not sufficient to support such an analysis.

We conclude that antiarrhythmic therapy is likely to be effective if as many as 15 complexes are induced at therapy assessment in patients who have inducible sustained ventricular tachycardia. The best cutoff point for predicting efficacy of a tested therapy is difficult to identify because only a small fraction of trials have outcomes between 11 and 20 induced complexes. Patients in whom initiation of sustained ventricular tachycardia is not prevented are at high risk for arrhythmia recurrence and sudden death.

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