Recurrent Sustained Ventricular Tachycardia

3. Role of the Electrophysiologic Study in Selection of Antiarrhythmic Regimens

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SUMMARY Twenty patients with recurrent sustained ventricular tachycardia (VT) underwent serial electrophysiologic studies (EPS) 1) to determine the predictive value of the EPS in the selection of antiarrhythmic therapy, and 2) to establish the therapeutic efficacy of available antiarrhythmic agents. In each patient VT could be reproducibly initiated by programmed stimulation. After control EPS, the effects of several drugs (lidocaine, procainamide, quinidine, disopyramide and diphenylhydantoin) on the ability to initiate VT were assessed. An oral regimen was chosen on the basis of acute EPS and its effectiveness was evaluated by repeat EPS in 24-72 hours. Blood levels achieved acutely were used as guidelines to chronic therapy.

In 14 patients the initiation of VT was prevented by the acute administration of one or more agents. In 13 of these patients, a chronic oral regimen based on these results prevented recurrence of VT with a three- to 27-month follow-up. In the remaining patient, oral therapy could not achieve blood levels of procainamide shown to be effective intravenously, and VT recurred. In six patients no single drug or drug combination was effective during acute EPS, and VT recurred in all while on therapy with the agent shown to make initiation of VT most difficult. Procainamide prevented VT in nine patients; quinidine in three patients; lidocaine in three patients; disopyramide in two patients; and diphenylhydantoin in one patient. The mean duration of EPS studies was 4.5 days.

This study suggests that serial EPS provides rapid identification of successful antiarrhythmic therapy and can predict in which patients conventional therapy would be ineffective, thereby identifying patients requiring more aggressive modes of therapy.

THE THERAPY OF RECURRENT sustained ventricular tachycardia (VT) is often frustrating and frequently unsuccessful. Recently, considerable emphasis in the therapy of this arrhythmia has been placed on surgical and pacemaker modalities, as well as investigational pharmacologic agents.1-8 A detailed investigation of the efficacy of the commonly available antiarrhythmic agents, however, has not been reported. The purposes of this study were: 1) to determine the predictive value of the electrophysiologic study in the selection of chronic antiarrhythmic regimens for the therapy of recurrent sustained VT, and 2) to establish the role of the more widely-used and currently available antiarrhythmic drugs.

Materials and Methods

Twenty patients with recurrent sustained VT underwent serial electrophysiologic studies to test the efficacy of several antiarrhythmic drugs and were then followed prospectively on a chronic regimen devised on the basis of the results of these studies. The studies were performed after informed consent was obtained in the nonsedated, postabsorptive state. All patients had had at least four documented spontaneous episodes of symptomatic VT (13 ± 5, mean ± SD) that were sustained for minutes to days and usually required pharmacologic or electrical conversion. One to 25 (mean 5) hospitalizations and 9 ± 4 (mean ± SD) cardioversions had been required for therapy of VT before these electrophysiologic studies. Seventeen of the patients were referred because they were considered refractory to conventional drugs.

In the 17 patients referred for medically refractory VT, lidocaine and procainamide had been used unsuccessfully. Doses of procainamide ranged from 3-6 g/day, but in most cases blood levels were not available. Twelve patients had received quinidine before study and none had been treated with disopyramide. Three patients had been unsuccessfully treated with diphenylhydantoin before referral.

The clinical data which characterize this group are detailed in table 1. The mean age of the patients was 54 years (range 8-67 years). Eighteen (90%) patients had organic heart disease, primarily coronary artery disease. Thirteen of these patients had a ventricular aneurysm. Two patients (10%) had VT without structural heart disease as documented by a normal echo-
cardiogram, exercise test, and hemodynamic and angiographic catheterization.

Electrophysiologic studies were performed with multiple electrode catheters inserted either percutaneously or by cutdown and positioned in the heart under fluoroscopic guidance. Quadripolar electrode catheters were used when recording and stimulation from a site was required. The distal electrode pair was used for stimulation and the proximal pair for recording. Intracardiac recordings were filtered at 40-500 Hz and simultaneously displayed with two or three electrocardiographic leads on a multichannel oscilloscope (E for M, DR-16, White Plains, NY). The data were stored on magnetic tape and later retrieved on photographic paper at speeds of 100-400 mm/sec.

Programmed electrical stimulation (PES) was performed using a specially designed programmable stimulator and isolated constant current source (Bloom Associates Ltd., Narberth, PA). The stimuli were rectangular pulses, 1 msec long and twice diastolic threshold during the initial and serial studies. The paired t test was used for statistical analysis.

The stimulation protocol during control and all subsequent studies included the introduction of single and double ventricular extrastimuli during normal sinus rhythm, single and double extrastimuli during ventricular pacing at several cycle lengths and ventricular pacing at cycle lengths of 600-250 m sec for 15-60 seconds. This protocol has been described in detail previously. A single premature ventricular stimulus (S2) was introduced in late diastole during sinus rhythm or ventricular pacing (cycle lengths of 600 and 500 in all patients, and in selected patients basic cycle lengths ranged from 400-1000 m sec) and moved earlier until ventricular refractoriness was encountered. Double premature stimuli (S2, S3) were introduced starting at an S1-S2 interval 50-100 m sec longer than the ventricular refractory period and an S2-S3 equal to S1-S2. S2-S3 was shortened until S3 failed to capture the ventricle, and S1-S2 was then shortened until S2 could evoke a response. This was continued until both S2 and S3 reached refractoriness. For serial studies, a quadripolar catheter usually introduced via an antecubital vein was positioned at the right ventricular apex.

In each patient, VT similar in morphology and rate to the spontaneously occurring arrhythmia could be reproducibly initiated and terminated by programmed ventricular stimulation. During control studies the mechanism of VT was characterized and the site of origin was defined by endocardial mapping as previously described. Serial electrophysiologic studies were then performed after the administration of two or more drugs. In 16 patients at least three drugs were evaluated. During these studies clinical status was stable, serum electrolytes were maintained within the normal range and other medications were unchanged. In no patient was VT related to transient states such as ischemic episodes, exercise, drug toxicity or congestive heart failure. The drugs studied in each patient are shown in table 2. Certain drugs were not studied in selected patients because of previously

<table>
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<tr>
<th>Pt</th>
<th>Age/Sex</th>
<th>Cardiac diagnosis</th>
<th>ECG</th>
<th>Ventricular tachycardia</th>
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<td>CL (msec) Site of origin</td>
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<td>IMI, TPMI</td>
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</tr>
<tr>
<td>20</td>
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<td>ASHD, LV An</td>
<td>AMI, RBBB, LAHB</td>
<td>470 LV</td>
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</table>

Abbreviations: ALMI = anterolateral myocardial infarction; AMI = anterior myocardial infarction; ASHD = atherosclerotic heart disease; ASMI = anterosetal myocardial infarction; CCM = congestive cardiomyopathy; CL = cycle length; F = female; IACD = intra-atrial conduction defect; IMI = inferior myocardial infarction; IVCD = intraventricular conduction defect; LAHB = left anterior hemiblock; LBBB = left bundle branch block; LV = left ventricle; LV An = left ventricular aneurysm; LVH = left ventricular hypertrophy; M = male; MR = mitral regurgitation; PEHD = primary electrical heart disease; RAD = right axis deviation; RBBB = right bundle branch block; RHD = rheumatic heart disease; RV = right ventricle; TPMI = true posterior myocardial infarction; WNL = within normal limits.
documented toxicity or allergy, contraindications or clinical status.

**Serial Drug Protocol**

Drugs were administered in the following manner:

1. Lidocaine 5 mg/kg intravenously over 15 minutes; administration was discontinued if significant neurologic side effects occurred.
   
2. Procainamide 50 mg/min intravenously to a total dose 1000, 1500 or 2000 mg, until VT could no longer be initiated by PES or until either hypotension (below 90 mm Hg systolic) or QRS prolongation of greater than 50% occurred.
   
3. Quinidine gluconate 800 mg intramuscularly or quinidine sulfate 1.6–2 g orally over 24 hours.
   
4. Disopyramide 200–300 mg orally as a loading dose and 100–150 mg every 6 hours maintenance.
   
5. Diphenylhydantoin 20 mg/min intravenously (maximum dose 1000 mg).

PES was performed immediately at the termination of procainamide, lidocaine and diphenylhydantoin infusions, 60–90 minutes after quinidine administration, and 48 hours after the initiation of disopyramide administration. Plasma concentrations of procainamide, N-acetylprocainamide, quinidine and diphenylhydantoin were measured immediately after terminating the programmed stimulation protocol or at the time of induction of VT if it occurred. Except for lidocaine and procainamide, which were studied on the first day (procainamide 30–45 minutes after lidocaine), only one drug was studied each day. Before study of each agent (including between lidocaine and procainamide), VT was initiated by PES to confirm return to the control state, and plasma concentrations were measured to document elimination of the previously studied drug. In patients in whom several dosages of the same drug were evaluated, PES was performed after each incremental administration (e.g., if a patient received 2000 mg procainamide intravenously, PES was performed after 1000, 1500 and 2000 mg). If no single agent was effective, combination regimens were evaluated (see Results section). Propranolol was not tested routinely because contraindications were present in the majority of patients. An agent suitable for a chronic oral regimen was identified and initiated. After 48–72 hours of this regimen, PES was performed at a time of lowest predicted blood level of the selected drug to confirm effect of the oral regimen. During the course of these serial studies each patient was continuously monitored in an intensive care unit.

Patients underwent 24-hour continuous ambulatory electrocardiographic monitoring and treadmill exercise testing before discharge and were seen no less frequently than at three-month intervals by one of the investigators or their private physician. If the patient was unable to return for examination, the records of patients evaluated by private physicians were used. Patients were evaluated for freedom from previous symptoms of VT during follow-up.

**Definitions**

1) Sustained VT: VT which lasted longer than 1 minute or required termination before that time by PES or cardioversion.

2) Non-sustained VT: VT which spontaneously ter-
minimized in 10 or less complexes. (In these patients no episode of VT was self-terminated after 10 complexes).

3) Inducibility: VT was considered easier to induce when compared to control if the tachycardia zone was increased or if an extrastimulation technique which could not induce VT during control conditions was able to induce it after drug administration. Conversely, VT was considered more difficult to induce if the opposite effects were produced by the drug.

Results

In all 20 patients sustained VT was initiated by either single or double programmed extrastimuli during the control study and before each acute drug evaluation. Although some slight variability (10-20 msec) in the coupling intervals (S1-S2 and/or S2-S3) required to induce VT was observed during control studies from day to day, the mode of induction (i.e., single or double stimuli) did not change. No significant changes in the morphology or cycle length of the induced VT occurred during serial control studies. VT was usually terminated by programmed stimulation as previously described. Cardioversion was required on four occasions in three patients during these studies.

These studies required an average of 4.5 days to perform. Electrode catheters remained in place from 1-10 days and occasionally required repositioning (two patients) or replacement (one patient). One patient developed deep vein thrombophlebitis in a femoral vein; however, in this patient the electrode catheter used for serial studies was in an antecubital vein. Two patients developed superficial phlebitis at the site of catheter insertion. No complications occurred in any other patient.

The effects of procainamide and lidocaine were studied in each patient. In addition, quinidine was studied in 12 patients, disopyramide in five patients and diphenylhydantoin in seven patients. Four drugs were studied serially in eight patients, three drugs were studied in eight patients, and two drugs were studied in the remaining four patients.

The induction of sustained VT was prevented in 14 patients after the acute administration of one or more drugs (table 2). In 13 of these patients a chronic oral regimen was instituted which was also able to prevent the induction of VT by PES (group A). In one patient (case 19) the trough plasma level of procainamide attained even on a 3-hour schedule of oral administration was less than that shown to be effective intravenously and was inadequate to prevent the initiation of VT. In six patients no single drug or combination of agents was able to prevent the initiation of VT. These latter six patients and case 19 constitute group B. The plasma concentrations attained in all patients are in table 3.

Group A — 13 Patients

Inability to Induce VT

In nine patients at least one drug completely prevented the initiation of VT (table 2, fig. 1). The inability to induce VT usually depended on plasma concentration (fig. 2). Two patterns of response to increasing concentrations were observed. In three patients, as the drug concentration increased, the tachycardia became progressively more difficult to induce and finally could not be produced by any stimulation technique. As the tachycardia became more difficult to induce, its cycle length usually increased. In six patients, as the concentration of a particular drug was increased, the ventricular refractory period increased and the VT was more easily induced; however, it had a longer cycle length. This pattern persisted until at a certain concentration the VT was no longer inducible (fig. 2). This latter pattern was observed after the administration of procainamide, quinidine or disopyramide, but not lidocaine or diphenylhydantoin.

Inability to Induce Sustained VT

In four patients at least one drug prevented the initiation of sustained VT. Repetitive ventricular responses (fewer than 10 complexes) similar in morphology to those of spontaneous VT could be induced by PES. Each episode stopped spontaneously in these patients. This pattern was a distinct change from control in that VT during control studies was sustained once initiated in these patients. In these four patients no plasma drug concentration was achieved orally or without side effects which was able to prevent the induction of all reentrant responses.
Figure 1. Serial electrophysiologic study of ventricular tachycardia (VT) in a representative group A patient (case 11). In each panel electrocardiographic lead V₁ and a right ventricular electrogram (RV) are shown. Stimuli during ventricular pacing (S₁) and programmed extrastimuli (S₂, S₃) are indicated. The coupling intervals of the extrastimuli are shown on the left between S₁–S₂ and S₂–S₃. The tachycardia cycle length is indicated on the right. In panel A, the control study, VT was initiated by two extrastimuli and the cycle length was 270 msec. In panel B, after the intravenous administration of 1500 mg of procainamide (18.7 μg/ml), VT was still inducible at slightly longer coupling intervals; however, the tachycardia cycle length was markedly prolonged. The QRS complex was also widened to 215 msec (control 165 msec). In panel C, after oral administration of 2000 mg of quinidine (3.4 μg/ml), VT was inducible at the control coupling intervals and the cycle length was not significantly different from control. In panel D, after intravenous administration of 175 mg of lidocaine, non-sustained VT (one complex) was induced. In panel E, after intravenous administration of 1000 mg of diphenylhydantoin (9.75 μg/ml), two ventricular extrastimuli resulted in no VT complexes. No other coupling intervals or stimulation protocol produced VT after diphenylhydantoin. Identical results were obtained three days later during chronic oral administration of diphenylhydantoin (10.5 μg/ml).
In each of these 13 patients, the effects produced by an acutely administered drug were reproduced by an oral regimen. This effect was verified by a final electrophysiologic study performed at the time of lowest plasma concentrations of the drug.

**Group B — Seven Patients**

**Failure to Prevent Initiation of VT**

In seven patients no drug or combination of drugs was able to prevent the initiation of VT (group B). Although certain agents made the tachycardia more difficult to initiate and the tachycardia rate slower, sustained VT was produced in each patient on all drugs tested (fig. 3). In one patient (case 19), although intravenous procainamide was able to prevent induction of VT at a blood level of 24.4 µg/ml, a chronic oral regimen could not be devised which produced this plasma level without toxicity. In this patient on the maximally tolerated oral procainamide dose (trough plasma levels 11.4–12.8 µg/ml procainamide, 5.7-6.7 µg/ml NAPA), PES produced VT (fig. 4).

In these seven patients, several combination regimens were evaluated after the failure of single agents to prevent the initiation of VT. These regimens included: procainamide and quinidine (four patients), procainamide and disopyramide (two patients), procainamide and lidocaine (five patients), procainamide and diphenylhydantoin (two patients), and procainamide, diphenylhydantoin and lidocaine (two patients). No combination regimen prevented the initiation of VT in these patients.

**Effects of Specific Agents**

Procainamide increased the effective refractory period of the right ventricle in each patient (20–60 msec); quinidine and disopyramide produced less marked increases (10–30 msec) in this parameter. Lidocaine and diphenylhydantoin had no consistent
Control

Procainamide

Quinidine

Disopyramide

Lidocaine

**Figure 3.** Serial electrophysiologic study in ventricular tachycardia (VT) in a representative group B patient (case 20). In each panel, electrocardiographic lead V1 and a right or left ventricular electrogram (RV or LV) are shown. Abbreviations, coupling intervals and cycle lengths are indicated as in the previous figures. In panel A, during the control study, VT was induced by a single extrastimulus during ventricular pacing. In panel A, after intravenous administration of 1250 mg of procainamide (11.3 μg/ml), VT was induced by a single extrastimulus during sinus rhythm and the cycle length was longer than control. The difference in QRS morphology in panel B is primarily due to a change in gain and QRS prolongation. In panel C, after oral administration of 2000 mg of quinidine (3.4 μg/ml), VT was initiated by a single extrastimulus during ventricular pacing and the cycle length was 730 msec. In panel D, after oral administration of disopyramide (200 mg loading dose and 400 mg in 24 hours), VT (cycle length 560 msec) was induced by a single extrastimulus during ventricular pacing. In panel E, after intravenous administration of 150 mg of lidocaine, VT was more difficult to induce, and required two extrastimuli; however, the tachycardia cycle length is shortened to 320 msec from a control of 470 msec. No antiarrhythmic agent at tolerated plasma concentrations prevented the initiation of VT.
effects on the right ventricular effective refractory period, and changes ranged from −20 to 20 msec.

The effect of specific drugs was random and unpredictable in each patient. Procainamide was the most frequently effective drug, preventing the initiation of sustained VT in nine of 20 patients (eight patients when administered orally). Quinidine was successful in preventing VT in three of 12 patients; however, eight patients were not tested with quinidine (five because of prior allergic or toxic reactions). In only one patient were procainamide and quinidine both successful. Disopyramide was successful in one of five patients in whom it was used. One of these drugs was successful in preventing the initiation of VT in 11 of the 20 patients. In individual patients in whom procainamide, quinidine or disopyramide did not prevent the initiation of VT, the tachycardia rate was almost always slower after the drug (procainamide in 10 of 11; quinidine in eight of nine; disopyramide in three of four). For the group the tachycardia cycle length slowed significantly after procainamide (P < 0.005), quinidine (P < 0.05), and disopyramide (P < 0.05) (table 4).

In three patients (3, 9 and 20), procainamide

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**Figure 4.** Inability to reproduce effects of intravenous procainamide with an oral regimen (case 19). In each panel electrocardiographic lead V1 and right ventricular (RV) electrogram are shown. The format is identical to figures 1-3. In panel A, during the control study, ventricular tachycardia (VT) was induced by double extrastimuli. The cycle length is 400 msec. In panel B, after 2000 mg of procainamide intravenously (24.4 μg/ml), VT was not inducible. No stimulation technique produced VT at this concentration. In panel C, during chronic oral procainamide therapy (8.5 μg/ml, NAPA 5.6 μg/ml), VT was induced by double stimuli; the cycle length is prolonged compared to control. In panel D, during chronic oral procainamide therapy at the maximally tolerated dose (12.8 μg/ml, NAPA 6.7 μg/ml), VT was initiated by a single extrastimulus during sinus rhythm. The cycle length was increased further to 540 msec and the QRS duration was increased to 230 msec (180 msec, control).
produced an incessant form of VT. In each patient, procainamide facilitated the induction of VT (initiation during sinus rhythm by single extrastimuli at long coupling intervals), although the tachycardia rates were slower. During the period of incessant VT, spontaneous initiation occurred within seconds of termination by PES. The initiation was caused by spontaneous changes in sinus cycle length or premature depolarizations. This incessant form disappeared as procainamide concentrations waned and VT was no longer easily induced by PES. Similar results were observed after quinidine in one patient (case 20).

Lidocaine and/or diphenylhydantoin prevented the initiation of VT by PES in only three of 20 patients. In another patient lidocaine increased the cycle length of the induced tachycardia. In five of our patients, however, the tachycardia cycle length was shorter after lidocaine administration (table 2). There was no significant difference from control in mean tachycardia cycle length after either lidocaine or diphenylhydantoin administration.

The electrophysiologic parameters which characterized VT during the control study (cycle length, site of origin, mode of initiation or termination, or tachycardia zone) did not correlate with the response of individual tachycardias to any particular drug. Previous drug histories were also unhelpful. Most patients who were controlled on procainamide or quinidine had received these drugs, although at lower doses before study.

**Follow-up**

Each patient was treated with a drug regimen based on the results of the serial electrophysiologic studies. In the 13 patients in whom an oral drug regimen prevented the initiation of sustained VT (group A), that regimen was used. We attempted to maintain chronic plasma drug concentrations at or above plasma levels which were effective during the acute serial studies (table 5). These patients have been followed for three to 27 months. So far, no drug has been discontinued in this group and no symptomatic side effects have occurred.

Two patients have had recurrences of VT. In both cases the patients were treated with procainamide and the referring physicians had reduced the procainamide dose before recurrence of VT. In neither case was the procainamide dose reduced because of clinical toxicity. In patient 10 the plasma concentrations on the reduced dose ranged from 5–8 µg/ml, while 14.2 µg/ml had been shown to be effective in preventing VT. In the other (patient 2), at the time of recurrence of VT the procainamide blood level was 6 µg/ml; 10.4

**Table 4. Tachycardia Cycle Length After Drug Administration**

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<td>Procainamide</td>
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<td>385 ± 71</td>
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<td>Quinidine</td>
<td>435 ± 92</td>
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<td>Diphenylhydantoin</td>
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**Table 5. Follow-up Data in Group A**

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<th>Chronic plasma concentration</th>
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<td>12.2 µg/ml</td>
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<td>Procainamide</td>
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<td>16.0–18.5 µg/ml</td>
<td>3 mos</td>
</tr>
</tbody>
</table>

* Died during follow-up (see text).
NA = plasma concentrations not available.
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unsuccessful would be necessary agents. A arrhythmic therapy with trant plasma levels likely that this reentrant premature ventricular depolarizations (>10/hr) occurred in nine of the 13 patients in group A before hospital discharge.

Two patients in group A died while on therapy. In one (case 1) death was due to glioblastoma multiforme six months after study. In the other patient (case 6) sudden death followed a rapid deterioration of chronic congestive heart failure and metastatic prostatic carcinoma.

The drug which made the tachycardia most difficult to induce and/or produced the lowest tachycardia rate was selected for chronic administration in the seven patients in whom no drug prevented the initiation of VT (group B). Each patient had either refused therapy with investigational drugs, a pacemaker or surgery, or conventional therapy had been chosen by the referring physician. In each patient VT occurred spontaneously within one to 22 days after the study (table 6). One of these patients (case 9) died after several episodes of VT which occurred in the hospital the day before scheduled ventricular aneurysmectomy. Another patient (case 17) died suddenly four months after study while on aprindine, which was begun after the recurrence of VT.

Discussion

The therapy of recurrent sustained VT is frequently unsuccessful and often requires protracted and repeated hospitalizations. Our study was designed to evaluate the ability of a protocol of programmed ventricular stimulation and serial pharmacologic interventions to develop rapidly a successful anti-arrhythmic regimen using commonly available anti-arrhythmic agents. A pharmacologic regimen can prevent spontaneous episodes of recurrent sustained VT by either suppressing the inducing stimuli (usually premature ventricular depolarizations) or altering the reentrant pathway so that it cannot sustain the arrhythmia. Since one premature ventricular depolarization is often sufficient to initiate VT, total abolition of premature ventricular depolarizations would be necessary to prevent VT reliably. It is unlikely that this is possible in most patients; however, successful electrophysiologic alteration of the reentrant pathway and abolition of the tachycardia might be achieved on a chronic basis despite failure to abolish isolated ventricular premature depolarizations.

Methodology of Serial Studies

The ability of a reentrant circuit to sustain VT can be assessed by PES, since premature ventricular stimuli introduced over a wide range of coupling intervals can be used to induce VT.9, 11, 13-16 PES provides a reproducible and readily available technique to assess the susceptibility of the reentrant pathway to sustained VT. Our data and that of Wu et al.,17, 18 Fisher et al.,19 and Hartzler and Maloney20 support the validity of applying the results of electrophysiologic studies to the therapy of clinical arrhythmias. The methodology of such studies is very important if the results are to be applicable to the clinical situation. When possible and safe, control studies should be performed on each day of the acute studies before the administration of the various drugs. This verifies the inducibility, morphology and rate of the tachycardia. Without these data, the effects of individual drugs cannot be accurately assessed. Equally important is the final electrophysiologic study performed several days after the institution of a chronic oral regimen. Programmed stimulation verifies that the oral regimen reproduces the effects of acute intravenous drug administration and that the trough plasma concentration is effective. The multiple control studies which document inducibility of the tachycardia over several days’ study validate the results of this last study, since a control study cannot be performed before that particular study.

In addition, the plasma drug concentrations should be measured at the time of the demonstrated electrophysiologic effect during the acute intravenous and chronic oral study. We have recently shown that the electrophysiologic effects of intravenously administered procainamide are closely related to plasma concentrations,21 and similar correlations should be expected with the other agents in this study. When a drug fails to prevent the initiation of VT, the concentration measurement verifies adequate drug levels. Finally, the plasma level attained before each study documents the absence of previously studied drugs and avoids the confusion of studying the combined effect of two agents.

<table>
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<th>Table 6. Follow-up Data in Group B</th>
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Abbreviation: VT = ventricular tachycardia.
Predictive Value of Serial Electrophysiologic Studies

Our data demonstrate that the efficacy of a variety of antiarrhythmic agents in the long-term prevention of recurrent sustained VT can be predicted by serial electrophysiologic studies. Furthermore, the plasma concentration of these agents can also be determined. In all 13 (100%) patients in whom the acutely administered drug prevented the induction of sustained VT and its effect could be reproduced by an oral regimen, VT was prevented during therapy with this agent at appropriate plasma concentrations.

Despite persistence of premature ventricular depolarizations in several of our patients, no sustained VT occurred during chronic therapy in group A. Furthermore, continuous electrocardiographic monitoring documented several brief, non-sustained episodes of VT (three to five complexes) in those patients in whom non-sustained VT could be induced by programmed stimulation (patients 2, 13 and 15). These observations support the concept that alteration of the reentrant circuit by the drug regimen, rather than suppression of premature ventricular depolarizations, is responsible for prevention of sustained VT.

We have used the plasma concentrations achieved by acute administration of antiarrhythmic drugs to devise oral regimens. Acute and chronic plasma levels, however, may not have similar antiarrhythmic effects because of metabolic alterations and delay in attaining chronic tissue concentrations. Nonetheless, the results of our studies show that these acute levels can accurately predict successful chronic levels. We cannot state that these levels are the minimally effective levels, since chronic electrophysiologic studies were not performed at several chronic blood levels. In the two patients (cases 2 and 10) in whom VT occurred spontaneously after reduction in procainamide dosage, the plasma concentrations were considerably below those previously shown to be effective during the acute serial studies.

It is possible that VT has occurred in those patients in whom successful regimens were devised; however, for several reasons we believe that this is not the case. In no patient studied was VT self-terminating if it persisted longer than 1 minute, whether before or after a drug administration. Second, only one patient (patient 20) was unable to recognize VT when it was induced during the chronic electrophysiologic studies even when the rate was markedly slowed by drugs. Finally, in each of the patients in whom a chronic regimen failed, the tachycardia was persistent, and the onset of VT was recognized by the patient even though in each case the VT was slower than during the control studies. Therefore, it is unlikely that prolonged episodes of VT have occurred unnoticed in these patients.

In addition to predicting the success of a particular regimen, our protocol accurately predicted failures. This ability has not been previously reported. In each patient in whom VT was initiated after administration of oral drugs, VT occurred spontaneously on the chronic regimen which had made initiation most difficult. Therefore, even on the most effective regimen, if VT was initiated by PES, spontaneous tachycardia occurred within 30 days. The ability to predict the failure of an antiarrhythmic regimen is important, because newer therapeutic modalities are becoming more available. These include investigational drugs, pacemakers and surgery (aneurysmectomy, transmyocardial incisions, etc). The early identification of those patients who are refractory to conventional therapy will allow prompt institution of a more aggressive regimen.

Efficacy of Commonly Available Antiarrhythmic Agents

The arrhythmia appeared to respond best to group 1A or membrane-depressant antiarrhythmic drugs, and procainamide was the most effective of that group. Wellens et al. compared the effects of procainamide, propranolol and verapamil and had similar results. Procainamide in their study prevented the initiation of VT in four of 12 (33%) patients, while propranolol and verapamil were unable to prevent the initiation of VT in those patients studied. In this study procainamide was able to prevent the initiation of VT in nine of 20 (45%) patients. The efficacy of procainamide in our study could be a result of the larger doses administered and higher plasma concentrations achieved. On the other hand, the group 1A agents were also observed to facilitate the initiation of VT in several patients. Since the initiation and maintenance of VT depends on a critical relationship between conduction velocity and refractoriness, it is not unexpected that an alteration in this relationship could facilitate as well as suppress the initiation of VT. Similar effects have been documented in other reentrant arrhythmias.

Lidocaine and diphenylhydantoin were only occasionally effective in preventing VT in this study. Although this result might appear contrary to the known ability of these drugs to terminate VT, Wellens et al. have shown that a drug's ability to terminate a tachycardia does not necessarily correlate with the ability to prevent its initiation. Recently El-Sherif and Lazzara have reported that lidocaine and diphenylhydantoin depress conduction in ischemic tissues in intact experimental animals. They postulated that these agents should thus slow tachycardia rates if the initiation of the tachycardia is not prevented. Our results do not support this contention. The tachycardia rate was slowed in only one patient after lidocaine or diphenylhydantoin administration. In fact, lidocaine increased the rate of the tachycardia in five patients (fig. 3). This effect could be caused by depression of conduction in a limb of a reentrant circuit and continuation of the reentry over another potential pathway which is shorter. The cycle length shortening could also be due to an increase in conduction velocity and/or shortening of ventricular refractoriness within the reentrant circuit. Such an improvement has been postulated by some as the mechanism of action of these drugs.
Value of Serial Electrophysiologic Studies

Many of our patients who had been characterized as refractory were eventually controlled by drugs which they had previously received (11 of 17 patients). Although each agent in this study is known to be effective against recurrent sustained VT, the selection of a drug and its dose in each patient is empirical and usually based on trial and error. This process can lead to prolonged hospitalizations and frequent rehospitalizations when regimens fail. Winkle et al. using an intensive clinical protocol evaluating several drugs in the treatment of recurrent VT required an average of 18 days to devise effective regimens. Furthermore, in their study only two of six (33%) patients with sustained VT were ultimately controlled with drugs. In contrast, the average duration of hospitalization required for our protocol was 4.5 days. We were able to control VT in 13 of 20 (65%) with drugs alone.

In summary, this study suggests that serial acute electrophysiologic studies evaluating several antiarrhythmic drugs facilitates the prescription of a successful chronic regimen and may identify those patients in whom conventional therapy would be ineffective. These patients might be appropriate candidates for more aggressive modes of therapy. This study provides further support for approaches to therapy of recurrent reentrant tachyarrhythmias recently advocated by others, and expands the usefulness of the cardiac electrophysiology laboratory to the clinician.

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