Sustained ventricular tachycardia in patients with idiopathic dilated cardiomyopathy: electrophysiologic testing and lack of response to antiarrhythmic drug therapy

DAVID S. POLL, M.D., FRANCIS E. MARCHELINSKI, M.D., ALFRED E. BUXTON, M.D., JOHN U. DOHERTY, M.D., HARVEY L. WAXMAN, M.D., AND MARK E. JOSEPHSON, M.D.

ABSTRACT Eleven consecutive patients with idiopathic dilated cardiomyopathy and spontaneous, sustained ventricular tachycardia (VT) of uniform morphology underwent programmed ventricular stimulation and serial antiarrhythmic drug testing. The mean ejection fraction was 30 ± 6.4%. Sustained VT was induced by programmed electrical stimulation in all 11 patients. A mean of 3.7 ± 2.4 antiarrhythmic drugs were evaluated by programmed stimulation, including at least one experimental agent in eight patients. In nine of 11 patients VT remained inducible on all drug therapy. During a mean follow-up period of 21 ± 14 months there were four sudden deaths and two patients with recurrences of VT. In all six patients with sudden death or recurrence of VT, the arrhythmia remained inducible on drug therapy. Three patients who died suddenly had a hemodynamically stable, induced tachycardia on antiarrhythmic therapy. Of eight patients treated with amiodarone, only two were successfully treated. We conclude that in patients with sustained VT and idiopathic dilated cardiomyopathy, VT can be induced by programmed electrical stimulation. VT will usually remain inducible on antiarrhythmic therapy, and sudden death can occur despite slowing and improved tolerance of the induced arrhythmia. Amiodarone may have limited efficacy, and more aggressive therapy, such as surgery or implantation of an automatic internal defibrillator, should be considered in this patient population.

rhythmic agents had been discontinued for at least five half-lives in nine patients and during treatment with procainamide for attempted control of frequent recurrent VT in two patients.

Stimulation was performed with a custom-designed, programmable stimulator (Bloom Associates, Ltd.). With a constant current source, rectangular impulses of 1 msec duration were delivered at twice diastolic threshold. Recordings were made with a 16-channel physiologic recorder (VR-16; Electronics for Medicine), and real-time records were obtained with an ink-jet recorder (Siemens Elema Mingograf) at a paper speed of 100 to 200 mm/sec.

Our stimulation protocol has been reported in detail. Briefly, ventricular extrastimuli were introduced during at least two ventricular paced cycle lengths (S1-S2 interval usually 600 and 400 msec), beginning late in diastole and moving progressively earlier until ventricular refractoriness was reached. If a single extrastimulus (S1) did not induce VT, a second extrastimulus (S2) was added. Double extrastimuli were introduced, starting with an S1-S2 interval 50 to 100 msec greater than the ventricular effective refractory period and S1-S2 equal to the S1-S2 interval. S2-S3 was shortened by 10 msec decrements until S1 became refractory, at which time S2 was decreased by 10 msec decrements until S1 evoked a response. This sequence was repeated until both extrastimuli reached refractoriness or sustained VT was induced. Stimulation was initially performed from the right ventricular apex. If VT was not initiated at this site, single and double ventricular extrastimuli were then introduced from the right ventricular outflow tract. Incremental ventricular pacing was then performed at cycle lengths of 350 to 250 msec for at least 20 cycles at each paced cycle length. If this failed to initiate VT, a third extrastimulus was added and programmed stimulation repeated in a similar fashion at the right ventricular apex at two paced cycle lengths, and then at the right ventricular outflow tract. Left ventricular stimulation with the same protocol was performed in two patients in whom right ventricular stimulation failed to induce sustained VT.

Patients underwent repeat programmed stimulation after at least five half-lives of selected antiarrhythmic drugs. Routinely, antiarrhythmic agents were administered in the following manner. Procainamide was given either as an intravenous infusion at a rate of 50 mg/min to a total dose of 1 to 2.5 g or orally at a dose of 0.5 to 1.5 g every 4 hr. Quinidine sulfate was given at a dose of 200 to 400 mg orally every 6 hr. Disopyramide was given in doses of 100 to 200 mg orally every 6 hr. Phenytoin (Dilantin) was given orally 300 to 400 mg daily after a 1 g loading dose. Mexiletine was given orally 100 to 300 mg every 8 hr. Aprindine was given orally 100 to 200 mg every 8 hr. Propafenone was given intravenously at a dose of 2 mg/kg. Amiodarone was given orally in a dose of 1400 mg/day for 1 week and then as a daily dose of 200 to 800 mg. The maximum dose of antiarrhythmic agents was determined by the end points of either eradication of clinical or inducible VT, hypotension, QRS prolongation >50% over control, or development of intolerable side effects.

Data analysis and follow-up. Continuous data are expressed as mean ± SD. We compared the mode of induction at baseline study and on the antiarrhythmic regimen at discharge. VT was considered "easier" to induce on discharge antiarrhythmic medication compared with baseline when fewer extrastimuli, longer extrastimulus coupling intervals, and longer paced cycle lengths were used to initiate the tachycardia, and/or when initiation occurred with right ventricular stimulation when left ventricular stimulation was required in the baseline study. Additionally, initiation of VT by rapid ventricular pacing was considered an "easier" form of stimulation than triple extrastimuli based on prior data.

Follow-up information was obtained at repeat visit to the Arrhythmia Evaluation Center at the Hospital of the University of Pennsylvania, or, when patients lived a long distance from the center, by telephone conversation with the patient and the patient's private physician. Details regarding medication compliance, changes in therapy, recurrence of tachycardia, and death were obtained. Sudden cardiac death was defined as death occurring within one-half hour of the onset of symptoms in a patient free of symptoms during the preceding 24 hr and in whom no other cause of death was discernible.

Results

Clinical characteristics (table 1). The mean ejection fraction of the group was 30 ± 6.4% (range 20% to 39%). Coronary angiographic studies in nine patients revealed no significant coronary artery disease.

Electrophysiologic testing (table 2)

Induction of VT. Sustained VT was induced in all 11 patients. Nine of the 11 patients had sustained VT of uniform morphology at initial testing. Two of the nine patients (Nos. 1 and 8) underwent initial testing while on therapy with procainamide for attempted control of intractable VT. In one patient (No. 3) nonsustained VT was induced during baseline study and uniform sustained VT identical to that observed clinically was induced while the patient was on procainamide, the drug taken at the time of clinical arrhythmia presentation. In a second patient (No. 4) VT was not induced in the baseline study. However, stimulation in this patient did not include triple extrastimuli. With the patient on antiarrhythmic therapy (procainamide and aprindine), uniform sustained VT was induced with programmed stimulation. Spontaneous VT had been previously observed with the patient in the drug-free

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/sex</th>
<th>EF (%)</th>
<th>Coronary angiography</th>
<th>NYHA functional class</th>
<th>Baseline ECG</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>46/M</td>
<td>34</td>
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<td>IVCD</td>
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<td>37</td>
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<tr>
<td>10</td>
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<td>22</td>
<td>ND</td>
<td>III</td>
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<tr>
<td>11</td>
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<td>29</td>
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<td>IVCD</td>
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EF = ejection fraction; ECG = electrocardiogram; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; NYHA = New York Heart Association; ND = not done; RBBB = right bundle branch block.
state and during treatment with quinidine, procainamide, lidocaine, and disopyramide.

One patient demonstrated three morphologically distinct VTs, six patients demonstrated two morphologically distinct VTs, and four patients demonstrated a single type of VT in response to programmed stimulation.

Sustained VT was induced by a single ventricular extrastimulus in one patient, double extrastimuli in four patients (one by left ventricular stimulation only), triple extrastimuli in five patients, and rapid pacing of the left ventricle in one patient. Twelve-lead electrocardiograms of the spontaneous clinical tachycardia were available in eight patients. In seven of these patients one of the induced VT morphologies exactly matched the clinical VT with respect to the type of bundle branch block pattern and frontal plane axis.

**Termination of VT.** Pacing techniques were successful in terminating induced VT in eight of the 11 patients during the baseline study or subsequent drug trials. Rapid ventricular pacing terminated VT in seven patients, and ventricular extrastimuli terminated VT in one patient. Five patients received single ventricular extrastimuli over an entire range of coupling intervals during episodes of VT. In four of these five patients, resetting occurred over a zone of premature stimulus coupling intervals.

**Assessment of antiarrhythmic drug efficacy.** All patients underwent serial drug testing with a mean of 3.7 ± 2.4 antiarrhythmic agents, and at least one experimental agent in eight patients (table 3). Sustained VT remained inducible with all drugs tested and with the final discharge antiarrhythmic regimen in nine of the 11 patients (table 2). In all instances, one of the tachycardias induced on drug therapy matched a morphologic type induced at the baseline study. In two patients

<table>
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<th>TABLE 2</th>
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<tr>
<td>Response to programmed stimulation</td>
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<tr>
<td><strong>Mode of VT induction</strong></td>
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<tr>
<td><strong>Drug at baseline study</strong></td>
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A = amiodarone; Ap = aprindine; CV = cardioversion; CL = cycle length; LBBB = left bundle branch block; LV = left ventricle; M = mexiletine; NSVT = nonsustained VT; PCL = paced cycle length; P = procainamide; Q = quinidine; RP = rapid pacing; RBBB = right bundle branch block; RV = right ventricle; RVA = right ventricular apex; RVOT = right ventricular outflow tract; S = sustained; VES = ventricular extrastimuli; sup. = superior; inf. = inferior; horiz. = horizontal.

*A* Serum procainamide level 9.2 µg/ml.

*P handlers* Serum procainamide level 18.0 µg/ml.
only nonsustained VT was induced with programmed stimulation; one (patient 3) was on quinidine and the other (patient 4) was on amiodarone. The latter patient had a recurrence of VT while taking amiodarone and was placed on aprindine, which did not prevent induction of a slow, hemodynamically tolerated tachycardia.

Additional therapy. Two patients (Nos. 1 and 7) underwent implantation of automatic internal defibrillators; one (No. 7) had also undergone surgical resection and cryoablation (guided by catheter and intraoperative mapping) of the region of earliest electrical activity after the arrhythmia had recurred on all forms of medical therapy, including amiodarone.14 Although no arrhythmias recurred after surgery while the patient was on quinidine, the defibrillator was implanted because of drug-induced myocardial depression necessitating withdrawal of quinidine therapy. The defibrillator has effectively terminated clinical occurrence of arrhythmias in this patient.

Follow-up and relationship to inducibility of VT and mode of induction. During a mean follow-up period of 21 ± 14 months (range 9 to 49) there were four sudden deaths and two patients experienced recurrence of VT (table 3). All sudden deaths occurred within 13 months.

In all six patients with either sudden death or recur-
easier to induce sustained VT in patients with coronary artery disease, especially those with aneurysms, than in patients with other cardiac diseases. Naccarelli et al. studied 37 patients with cardiomyopathy, of whom 30 had dilated cardiomyopathy defined as cardiomegaly and diminished left ventricular contractility. Twenty-five of the patients with cardiomyopathy had clinical sustained VT and only six (24%) had sustained VT induced with a protocol that included single and double ventricular extrastimuli. It is not stated in their report what percentage of the patients with congestive cardiomyopathy had spontaneous, sustained VT, whether the tachycardia was uniform, or how many in this subset of patients had VT induced with programmed ventricular stimulation. Other studies of VT have included few patients with dilated cardiomyopathy, and specific details regarding their response to programmed electrical stimulation and definition of disease are lacking.

The reproducible induction and termination of ventricular tachycardia with programmed stimulation, the response to stimulation during VT, and the infrequency with which rapid pacing induced VT support reentry as the mechanism for the arrhythmia. These findings make less likely the possibility that triggered activity caused by delayed afterdepolarization is the mechanism, although it cannot be totally excluded.

Arrhythmia substrate. The anatomic substrate for VT in most patients with chronic coronary artery disease is a large myocardial infarction with subsequent formation of ventricular aneurysm. Arrhythmia in most patients with coronary artery disease appears to arise from a subendocardial site and is amenable to surgical therapy involving subendocardial resection. The substrate for VT in patients with idiopathic dilated cardiomyopathy has not been characterized. However, pathologic studies in patients with congestive cardiomyopathy have confirmed endocardial scarring as a common finding, and it is possible that discrete foci amenable to surgery will be found. One patient (No. 7) in our series underwent surgical excision and cryoablation of the region of myocardium that demonstrated presystolic electrical activity during intraoperative epicardial and endocardial mapping. VT, although inducible postoperatively without antiarrhythmic drugs, became noninducible while the patient was on quinidine. Worsening of congestive heart failure precluded continued therapy with quinidine. An automatic internal defibrillator was implanted and has been required one time in the past year. Thus standard endocardial surgery with or without cryoablative techniques may alter the substrate of VT, but the diffuse nature of the process would theoretically make recurrences from other areas possible.

Response to antiarrhythmic therapy. We found a particular refractoriness to antiarrhythmic drug therapy in our patients. More importantly, antiarrhythmic drug therapy including amiodarone failed to prevent clinical recurrence or sudden death in six of 11 patients. Alarming, sudden death occurred despite demonstration of a slower, well-tolerated VT induced by programmed electrical stimulation in three patients. Although it appeared that “easier” inducibility on the discharge antiarrhythmic medication was associated with a worse prognosis with respect to the occurrence of sudden death and recurrences of VT, the number of patients evaluated precludes any definitive statement. Furthermore, change in the mode of induction has not yet been validated as a predictor of clinical efficacy in any patient population with arrhythmias. Persistent inducibility on antiarrhythmic agents and a high incidence of clinical recurrence or sudden death suggest that an automatic internal defibrillator, with or without surgery, should be considered in this patient population.

Thus, in patients with sustained VT and idiopathic dilated cardiomyopathy, sustained VT can be induced by programmed electrical stimulation and remains inducible despite vigorous antiarrhythmic therapy. Moreover, sudden death can occur despite slowing and improved tolerance of the induced VT. More studies are needed to elucidate the substrate for VT in this patient population and to determine interventions that can improve the poor prognosis. Amiodarone appears to have limited efficacy. Nonpharmacologic therapy should be considered as a primary modality in preventing sudden death.

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