Etiology, Warning Signs and Therapy of Torsade de Pointes
A Study of 10 Patients

Andre Keren, M.D., Dan Tzivoni, M.D., Dov Gavish, M.D., Joseph Levi, M.D., Shmuel Gottlieb, M.D., Jesea Benhorin, M.D., and Shlomo Stern, M.D.

SUMMARY  Torsade de pointes, also called atypical ventricular tachycardia (AVT), was diagnosed in 10 patients, nine on antiarrhythmic therapy and one with acute central nervous system damage. Four patients received quinidine and five disopyramide, either alone or in combination with amiodarone. AVT was dose-dependent in some, but in others, it started shortly after initiation of drug therapy (idiosyncrasy). All patients had QT prolongation longer than 0.60 second immediately before the onset of AVT. This measurement appeared to be a more sensitive predictor of the development of AVT than QTc prolongation or QRS widening. All patients also showed bradycardia before AVT onset. After therapy, the QT immediately decreased, while QTc and QRS remained prolonged for longer periods. Isoproterenol was effective in five of seven patients, but was contraindicated in two others. Ventricular pacing was used in four patients, including the two who did not respond to isoproterenol, and this abolished AVT promptly. Isoproterenol or pacing appear to be the therapy of choice for AVT, while the conventional drugs used to treat the usual form of ventricular tachycardia are not only ineffective, but even contraindicated.

QUINIDINE SYNCOPE due to paroxysmal ventricular fibrillation was first described by Selzer and Wray in 1964,1 but the distinctive features of this life-threatening arrhythmia were characterized somewhat later by Dessertenne2 and other French authors.3-7 The name “torsade de pointes” seems to describe satisfactorily the unique trait of changing QRS axis during the episodes of this arrhythmia, but in the English-language literature, atypical ventricular tachycardia (AVT) is becoming an accepted name. AVT was found to be induced mainly by quinidine4, 8-13 and by other antiarrhythmic and cardiac drugs such as procanamide,11, 14 disopyramide,15, 16 lidocaine11 and pronylamine.11 Occasionally, other drugs such as phenothiazines,17 as well as hypokalemia,4, 7 hypomagnesemia,4, 18 electrical ventricular stimulation,19 congenital QT prolongation syndrome,20 or acute central nervous system damage21 may precipitate AVT. The accepted warning sign for an impending AVT is a widening of the QRS complex22-25 which, if drug-induced, mandates interruption of therapy.

We describe 10 patients who developed AVT within

References
a period of 1 year. The ECG warning signs that preceded the AVT in these patients, especially the QRS width, the QT and the QTC intervals, are analyzed. The therapeutic approaches we and others have used are detailed.

### Methods

AVT was diagnosed during a 12-month period in 10 patients, nine females and one male, ages 44–84 years, who were hospitalized in our intensive coronary care unit. This unit is equipped with Mennen-Greatbach bedside monitors with a direct-signal system to a central ECG monitoring console with a delay output of 10 seconds. Eight patients had been hospitalized for recurrent atrial fibrillation or tachycardia, one patient for multiple ventricular premature complexes (VPCs) and one for acute myocardial infarction. Routine electrolyte levels were within normal limits. The associated diagnosis and other clinical data are summarized in table 1.

AVT was diagnosed when a series of ectopic ventricular complexes, usually four to 20 beats, with frequently undulating QRS axis and changing QRS configuration occurred. Heart rates were 150–300 beats/min, with marked variability during the episodes. In every case, a VPC with a long coupling interval, ranging from 0.44–0.68 second, initiated AVT. The episodes usually terminated spontaneously, often with a VPC intermediate in form between the QRS of the basic tracing and that seen during the AVT; sometimes, the final beat was identical to the initiating VPC. The longest spontaneously terminating run of AVT lasted 28 seconds. After termination, the episodes tended to recur unless treated2.8.9 (fig. 1).

The ECGs recorded before and after the AVT were analyzed for basic rhythm, ventricular rate, QRS width, QT and QTC intervals (Bazzett formula) and for associated electrical disturbances. The drug therapy given before the AVT and the response to the therapeutic measures were evaluated.

### Results

**Antiarrhythmic Drugs Given Before AVT (table 1)**

 Nine patients (cases 1–9) received antiarrhythmic drug therapy before the appearance of AVT. Quinidine sulfate was given to cases 1–4, disopyramide to cases 5–7 and a combination of disopyramide and amiodarone to cases 8 and 9. Case 10 suffered from transient central nervous system damage and had attacks of paroxysmal atrial tachycardia alternating with sinus bradycardia with constantly prolonged QT and QTC intervals; this patient did not receive any antiarrhythmic drug.

The antiarrhythmic drugs were given chronically to three patients. Case 1 received quinidine sulfate, 1.2

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<table>
<thead>
<tr>
<th>Pt</th>
<th>Diagnosis</th>
<th>AVT induced by:</th>
<th>ECG before AVT-inducing therapy</th>
<th>ECG before AVT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>QRS width</td>
<td>QT</td>
</tr>
<tr>
<td>1</td>
<td>RHD, MS, PAF</td>
<td>Q 1.4 g/day</td>
<td>0.07</td>
<td>0.44</td>
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<tr>
<td>2</td>
<td>IHD, PAF</td>
<td>Q 1.2 g/day</td>
<td>0.10</td>
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<td>3</td>
<td>IHD, AHT VPCs</td>
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<td>0.48</td>
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<tr>
<td>4</td>
<td>RHD, MS, SSS, PAF</td>
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<tr>
<td>5</td>
<td>RHD, MS, PAF</td>
<td>D 0.6 g</td>
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<td>0.30</td>
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<tr>
<td>7</td>
<td>AMI, PAF</td>
<td>D 0.6 g</td>
<td>0.11</td>
<td>0.40</td>
</tr>
<tr>
<td>8</td>
<td>RHD, MS, PAF</td>
<td>A 0.8 g/day</td>
<td>0.06</td>
<td>0.32</td>
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<td>9</td>
<td>RHD, MS, PAF</td>
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<tr>
<td>10</td>
<td>CNS-D, QT prolongation</td>
<td>Mean</td>
<td>0.07</td>
<td>0.40</td>
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<tr>
<td></td>
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<td>Mean</td>
<td>0.074</td>
<td>0.376</td>
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</table>

**Table 1. Clinical Data, ECG Characteristics and Therapy in 10 Patients with Atypical Ventricular Tachycardia**

<table>
<thead>
<tr>
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<td>Mean</td>
<td>0.074</td>
<td>0.376</td>
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**Abbreviations:** A = amiodarone; AVT = atypical ventricular tachycardia; AHT = arterial hypertension; AMI = acute myocardial infarction; At = atropine; AVB = atrioventricular block; CNS-D = central nervous system damage; D = disopyramide; I = isoproterenol; IHD = ischemic heart disease; MS = mitral stenosis; NR = nodal rhythm; PAF = paroxysmal atrial fibrillation; Q = quinidine; RHD = rheumatic heart disease; SR = sinus rhythm; SSS = sick sinus syndrome; VP = ventricular pacing; VPCs = ventricular premature complexes.
g/day, for several years and cases 5 and 6 received disopyramide, 300 mg/day, for 3 and 6 months, respectively. An increase of the doses of these drugs within the therapeutic range resulted in the appearance of AVT after 24-48 hours. Therefore, in these patients, AVT can be regarded as a dose-dependent phenomenon. In case 1, the quinidine level on the day of the AVT (7.0 μg/ml) was slightly above normal (range of normal 3.0-6.0 μg/ml). In cases 2, 3, 4 and 7, AVT developed 2-24 hours after beginning quinidine or disopyramide therapy and is therefore regarded as an idiosyncratic reaction. In cases 8 and 9, disopyramide, 300 mg/day, was given for a relatively long period (3 months and 6 months, respec-
tively), and AVT occurred after the addition of amiodarone, 800 mg/day, for 5 days in case 8 and 2 days in case 9.

**Baseline ECG and ECG Immediately Before AVT (tables 1 and 2)**

Nine patients suffered from recurrent supraventricular tachyarrhythmias and one patient had multiple VPCs. Before receiving the antiarrhythmic therapy or the particular dosage that caused AVT, the heart rate ranged from 65–90 beats/min (mean 74 beats/min), the width of the QRS complex ranged from 0.06–0.11 second (mean 0.074 second), the QT interval ranged from 0.30–0.48 second (mean 0.376 second) and the QTc ranged from 0.39–0.51 second (mean 0.450 second). These measurements were performed during periods of regular sinus rhythm.

Immediately before the initial AVT episode, all patients had a slow ventricular rate (40–65 beats/min). Seven patients had sinus bradycardia, one had nodal bradycardia, and two had atrioventricular blocks, third-degree in case 3 and second-degree, Mobitz type II in case 7. All patients had a widening of the QRS and a prolongation of QT interval and QTc. The width of the QRS complex increased by an average of 23%. The widening was 16% or less in cases 1, 4, 5 and 7, 20% in case 2 and 33–43% in cases 3, 6, 8 and 9. Case 10, who suffered from central nervous system damage, had a 14% increase of QRS width in the immediate pre-AVT period. The mean QT interval increased by 73% (range 0.60–0.70 second), whereas the mean QTc increased by 35.5% (range 0.52–0.71 second).

**ECG Immediately After Spontaneous Cessation of AVT (table 1)**

In six patients, the spontaneous cessation of the AVTs was followed by a transient acceleration of the ventricular rate compared with the pre-AVT period (increase from a mean rate of 54.5 beats/min to 87.1 beats/min) and shortening of the mean QT interval (from 0.67 to 0.43 second). The mean QTc interval was also shortened, from 0.63 to 0.51 second (fig. 2). In cases 3, 4, 7 and 10 in whom third-degree atrioventricular block, sick sinus syndrome, second-degree atrioventricular block and central nervous system damage were found, respectively, there was no increase in the heart rate or decrease in QT or QTc intervals after spontaneous cessation of AVT.

**Therapeutic Measures and Responses (tables 1–3)**

In six patients, DC shocks were repeatedly applied, but new episodes of AVT recurred in all. The DC shocks were used to stop long AVTs that led to loss of consciousness, or when AVTs deteriorated into uniform ventricular tachycardia (fig. 3) or ventricular fibrillation. Lidocaine was given to cases 1, 2, 3 and 8 through bolus injections of 100 mg and continuous infusions up to 3 mg/min; this drug was ineffective in all instances. Intravenous procainamide was tried in case 2 and was not only ineffective, but the frequency of the AVT episodes seemed to increase.

Atropine, as much as 1.5 mg i.v., was given to four patients but abolished the AVT in only one (case 1). In the three cases in whom atropine was ineffective, sinus node activity did not increase after its administration.

Isoproterenol (2–8 µg/min) was used in seven patients; this drug was effective in five patients in whom immediate disappearance of the AVT was observed, concomitant with a quickening of the heart rate in all five.

Ventricular pacing was applied to cases 2, 3, 4 and 7. In two, the AVTs were refractory to previous isoproterenol and in the other two, pacing was the first attempted mode of therapy, as isoproterenol was regarded hazardous because of recent myocardial infarction in case 7 and excessive hypertension in case 3. In these four patients all ventricular arrhythmias were abolished at a pacing rate of 88–105 beats/min, always using the lowest effective rate for abolishing the AVT. The pacing was continued for as long as 48 hours and the electrode was withdrawn after an additional 24 hours. In two of these patients, atrial pacing was tried, and although it was initially effective, ventricular pacing was preferred because of the unstable electrode position during atrial pacing.

**ECG Findings After Treatment of AVT (table 1)**

Immediately after initiation of the effective treatment (pacing, isoproterenol or atropine), the heart rate increased in all 10 patients, from a mean of 52.4 beats/min to a mean of 89.6 beats/min (an average increase of 71%). The QT shortened, from a mean of 0.65 second to a mean of 0.50 second (an average decrease of 23%). Two patients had a shortening of the QTc interval; in four it became longer and in four others, it did not change; the mean QTc was 0.61 second both before and after therapy. The QRS width narrowed in three patients, from a mean of 0.086 second to 0.073 second (a decrease of 15%). In the other five patients (including cases 2 and 4, in whom atrial pacing was applied initially), QRS width did not change, whereas in cases 3 and 7, in whom ventricular pacing was applied as initial therapy, the QRS complexes became broader with ventricular pacing.

In cases 2, 3, 4 and 7, the QT returned to normal within 24 hours after the quinidine or disopyramide treatment was stopped. These were the patients in...
whom the prolongation of the QT interval and the AVT appeared shortly after the beginning of the antiarrhythmic therapy.

In cases 1, 5 and 6, who received quinidine and disopyramide for long periods before the appearance of the AVT, the QT returned to normal values only after 2, 2 and 3 days, respectively, after cessation of drugs. In cases 8 and 9, who received a combination therapy of amiodarone and disopyramide, the prolongation of the QT interval lasted for 5 days after cessation of the drugs. In case 10, the QT interval prolongation persisted for 2 weeks.

After withdrawal of AVT-inducing drugs and cessation of therapeutic measures against the AVT, the initial supraventricular arrhythmias (atrial fibrillation or tachycardia) recurred in seven of nine patients. This occurred only after the QT regained its normal values (0.30–0.44 second) and the QTc decreased to 0.40–0.42 second.

**TABLE 3. Details on Response to Various Treatments in 10 Patients with Atypical Ventricular Tachycardia**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients receiving therapy</th>
<th>No. of patients with favorable response</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC shock</td>
<td>6</td>
<td>Transient effect in all</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Procainamide</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Atropine</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Ventricular pacing</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

**Discussion**

**Etiology and Mechanisms of AVT**

AVT is a life-threatening arrhythmia that usually occurs during quinidine therapy. However, in our study, only four of the 10 patients developed this complication while taking quinidine, whereas disopyramide caused AVT in three cases and a combination of disopyramide and amiodarone caused it in two others. The relatively high incidence of disopyramide-induced AVT is surprising; disopyramide induces AVT only in sporadic instances\(^{15, 16}\) and is regarded as safe and well-tolerated.\(^{20, 30}\) Although disopyramide is used much less frequently than quinidine in our service, a similar number of patients developed AVT on each drug during the 12-month period of this series. Amiodarone has been described to induce AVT only when given in association with other QT-prolonging drugs.\(^{31, 32}\) The addition of this drug to two of our patients who were already treated with disopyramide resulted in AVT. After the cessation of amiodarone, disopyramide alone did not induce AVT in these patients. The only patient who did not receive antiarrhythmic drugs before AVT was case 10, in whom acute central nervous system damage was followed by attacks of AVT; this occurrence has already been described.\(^{14, 21}\)

Both idiosyncrasy and dose-dependency are well-recognized causes of AVT,\(^{13, 14}\) and idiosyncrasy has been assumed to be the more frequent. However, AVT occurred as an idiosyncratic reaction in only four of our patients, whereas it was a dose-dependent phenomenon in five, and in two of these it resulted
Electrocardiographic Features

Widening of the QRS complex by 25–50% or QRS width reaching 0.16 second are signs of quinidine toxicity that mandate discontinuation of the drug because they indicate a high risk of developing ventricular tachycardia or fibrillation.22–25 Among the nine patients taking antiarrhythmic drugs in our group, five developed AVT despite a QRS complex widening of less than 20%; the widest QRS we observed was 0.12 second.

According to some investigators,22–25 prolongation of the QT interval with quinidine does not necessarily require modification of the therapy. Other authors who reported cases of AVT described prior QT prolongation but did not advocate a specific value beyond which the drug should be withdrawn. In our series, the most striking feature was the marked prolongation of the QT interval, to 0.60 second or greater; this prolongation preceded the AVT in all cases. Sclarovsky and co-workers14 described polymorphous ventricular tachycardia in some patients with QT interval shorter than 0.56 second. However, in their series, not all patients fulfilled the criterion of torsade de pointes, diagnosed only “when an undulatory rhythm with continuous change in direction (in QRS axis) was observed.”14 In our patients, the range of the QT interval before the AVT was relatively narrow (0.60–0.70 second) while the range of the QTc was wider (0.52–0.71 second). Furthermore, in all 10 patients effective therapy was followed by an immediate shortening of the QT but not of the QTc. Thus, the actual QT rather than QTc may be more reliable in heralding AVT and evaluating the efficacy of therapy. We suggest that an uncorrected QT greater than 0.60 second may be an indication that the patient is at increased risk and may warrant withdrawal of the drug used. However, further data are required to confirm this as an absolute proscission.

All of our patients had a slow heart rate before AVT. The prolonged QT with the antiarrhythmic agents reflects a delayed repolarization process, and bradycardia by itself has a similar effect.11 Thus, the combination of bradycardia and prolonged QT appears to produce a particular proneness to AVT. This may explain why none of our patients developed AVT during an attack of ectopic supraventricular tachycardia. Six of our patients had transient acceleration of the ventricular rate immediately after spontaneous cessation of the AVT. This seems to result from an increased intrinsic sympathetic activity secondary to the sudden decrease in the blood pressure during the AVT.34–38 However, a tachycardic response does not appear to be a prerequisite for spontaneous cessation of AVT episodes, as no increase of the ventricular rate was found after the spontaneous termination of the episodes in four of our patients, those with atrioventricular block, sick sinus syndrome or brain damage.

In case 2, 3, 4 and 7, who developed AVT as an idiosyncratic reaction, the return of the QT interval to normal was faster than in cases 1, 5, 6, 8 and 9, who had a dose-dependent AVT. All patients were free of supraventricular ectopic activity as long as the QT was prolonged; the recurrence of the initial supraventricu-
ular arrhythmia in seven patients occurred only after the return of the QT to normal.

Treatment of AVT

The therapy of AVT is aimed at shortening and unifying the prolonged and nonuniform repolarization, which is the basic electrophysiologic disturbance responsible for this arrhythmia. The use of conventional therapy for suppression of ectopic ventricular activity is therefore not only ineffective but may even aggravate the arrhythmia. Acceleration of the heart rate is the simplest and fastest mode for shortening the QT interval and for abolishing the temporal dispersion of repolarization present during AVT. Isoproterenol is the most commonly used drug for this purpose and was effective in five of the seven patients to whom it was given. Partial success with isoproterenol has been reported. Although isoproterenol can be easily and rapidly applied, it carries certain risk: It markedly increases myocardial oxygen demand and may cause a variety of peripheral vascular effects, and therefore should be avoided in patients with acute myocardial infarction, angina pectoris or high blood pressure.

Ventricular pacing for the treatment of AVT can be instituted safely and rapidly in intensive care units. It can be used safely in patients with active coronary disease, hypertension and atrioventricular block and in all patients in whom isoproterenol therapy is ineffective. Pacing also enables one to determine accurately the minimal rate at which the recurrence of AVT can be prevented. Although pacing from the atrium may be hemodynamically advantageous, the electrode anchoring in the ventricle is much more stable. The unsafety of the atrial electrode position for long-term pacing was demonstrated in our case 2, in whom AVTs immediately recurred during intermittent failures of atrial pacing.

We conclude that disopyramide, either alone or in combination with other QT-prolonging agents such as amiodarone, seems to increase the incidence of AVT. Prolongation of the actual QT above 0.60 second, rather than QTc or QRS widening, may be an important warning sign that requires modification of therapy. A combination of prolonged QT and bradycardia may be especially deleterious. For therapy of AVT, we suggest early institution of isoproterenol or ventricular pacing, which are the most effective means of increasing the heart rate and shortening the QT interval.

Acknowledgment

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References

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Intermediate-density Lipoprotein and Cholesterol-rich Very Low Density Lipoprotein in Angiographically Determined Coronary Artery Disease

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SUMMARY The relationship between the concentrations of intermediate-density lipoprotein (IDL) and other lipoproteins and the extent of coronary artery disease (CAD) was studied in 182 consecutive patients evaluated by selective coronary cineangiography. On univariate analysis, the extent of CAD correlated significantly and positively with very low density lipoprotein (VLDL) cholesterol, IDL cholesterol and low-density lipoprotein (LDL) cholesterol, and negatively with high-density lipoprotein (HDL) cholesterol. Analysis of four subgroups divided by IDL cholesterol and LDL cholesterol levels indicated that moderately increased levels of IDL cholesterol were closely associated with a high frequency of CAD. Moreover, multivariate regression analysis demonstrated that IDL cholesterol for men, LDL cholesterol for men and women and HDL cholesterol for men were significant variables of use in the final weighting procedure. IDL cholesterol was closely associated with cholesterol-rich VLDL. This study shows that IDL and cholesterol-rich VLDL combine to contribute to the development of CAD.

PLASMA LIPIDS and lipoproteins have been reported to be closely related to the development of coronary atherosclerosis.1-7 Plasma lipids are carried in the lipoproteins, each of which has a different effect on atherosclerosis.8 Therefore, the levels of individual lipoproteins are better predictors of coronary artery disease (CAD) than those of plasma lipids. Plasma lipoproteins are usually divided into five classes:8 chylomicrons, very low density lipoprotein (VLDL, d < 1.006), intermediate-density lipoprotein (IDL, d 1.006-1.019), low-density lipoprotein (LDL, d 1.019-1.063), and high-density lipoprotein (HDL, d 1.063-1.210). Recent studies emphasize that the concentrations of LDL correlate positively and HDL correlate negatively with CAD.1, 3, 6, 8

The relationship between VLDL and CAD has been less well defined.8, 10 In 1956, Gofman et al.11 reported that atherosclerosis, as manifested by definite evidence of CAD, was associated with an antecedent elevation of the serum S, 20-100 and possibly S, 12-20 lipoprotein (IDL). However, there have been few studies on IDL and the extent of CAD. Only case reports12 and few epidemiologic data are available.8 IDL and cholesterol-rich VLDL accumulate in abnormally high concentrations in the plasma of patients with type III hyperlipoproteinemia (broad β disease), which is highly associated with severe and premature atherosclerosis of coronary and peripheral arteries.13 Thus, it is suggested that IDL strikingly accelerates CAD.

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