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

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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.

Reference


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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 treated before AVT in 26. 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

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

<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>
</tr>
<tr>
<td>2</td>
<td>IHD, PAF</td>
<td>Q 1.2 g/day</td>
<td>0.10</td>
<td>0.44</td>
</tr>
<tr>
<td>3</td>
<td>IHD, AHT VPCs</td>
<td>Q 0.2 g/day</td>
<td>0.07</td>
<td>0.48</td>
</tr>
<tr>
<td>4</td>
<td>RHD, MS, SSS, PAF</td>
<td>Q 1.2 g/day</td>
<td>0.06</td>
<td>0.40</td>
</tr>
<tr>
<td>5</td>
<td>RHD, MS, PAF</td>
<td>D 0.6 g</td>
<td>0.07</td>
<td>0.36</td>
</tr>
<tr>
<td>6</td>
<td>IHD, PAF</td>
<td>D 0.6 g</td>
<td>0.06</td>
<td>0.30</td>
</tr>
<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>
</tr>
<tr>
<td>9</td>
<td>RHD, MS, PAF</td>
<td>D 0.6 g/day</td>
<td>0.07</td>
<td>0.32</td>
</tr>
<tr>
<td>10</td>
<td>CNS-D, QT prolongation</td>
<td>0.07</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>0.074</td>
<td>0.376</td>
<td>0.450</td>
</tr>
</tbody>
</table>
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-
Patients with QRS
1170
in tachyarrhythmias
800
QTc
of periods
Baseline
ranged from
0.30-0.48 second
(min).
Seven
blocks,
These
nodal
VPCs.
Before
damages
were
increased by
average
of
The
QTc.
AVTs was
9.
ATVTs was
beats/min)
and
1)
(table
ECG
Mobitz
type II
in case
7.
All patients had a widening
of
the
QRS
and
a
prolongation
of
QT
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
damages 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 procaainamide 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 abolised 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
therapy (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
came broader with ventricular pacing.

In cases
2, 3, 4 and
7,
the QT returned to normal
within
24 hours after the quinidine or disopyramide
therapy was stopped. These were the patients in

Table 2. Summary of Important ECG Measurements in 10 Patients with Atypical Ventricular Tachycardia

<table>
<thead>
<tr>
<th></th>
<th>In baseline</th>
<th>Immediately before AVT</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS (sec)</td>
<td>0.06–0.11 (mean 0.074)</td>
<td>0.07–0.12 (mean 0.091)</td>
<td>9–43% (mean 23%)</td>
</tr>
<tr>
<td>QT (sec)</td>
<td>0.30–0.48 (mean 0.376)</td>
<td>0.60–0.70 (mean 0.650)</td>
<td>33–113% (mean 70%)</td>
</tr>
<tr>
<td>QTC (sec)</td>
<td>0.39–0.51 (mean 0.450)</td>
<td>0.52–0.71 (mean 0.603)</td>
<td>4–55% (mean 35.5%)</td>
</tr>
</tbody>
</table>
whom the prolongation of the QT interval and the AVT appeared shortly after the beginning of the anti-arrhythmic 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 and is regarded as safe and well-tolerated. 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; 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 anti-arrhythmic 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.

Both idiosyncrasy and dose-dependency are well-recognized causes of AVT, 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...
from an assumed combined effect of amiodarone and disopyramide.

**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 proscription.

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.12 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, 35 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 supraventricular...
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.11, 18 The use of conventional therapy for suppression of ectopic ventricular activity is therefore not only ineffective but may even aggravate the arrhythmia.1, 11 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.6, 11, 14 Isoproterenol is the most commonly used drug for this purpose11, 17-19 and was effective in five of the seven patients to whom it was given. Partial success with isoproterenol has been reported.18 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.6, 12, 14, 16, 18, 20 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.14, 58 Although pacing from the atrium may be hemodynamically advantageous,40 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 AVT's 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.

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References

2. Dessertenne F: La tachycardie ventriculaire à deux foyers op-
Intermediate-density Lipoprotein and Cholesterol-rich Very Low Density Lipoprotein in Angiographically Determined Coronary Artery Disease

RYOZO TATAMI, M.D., HIROSHI MABUCHI, M.D., KOSEI UEDA, M.D., RYOSEI UEDA, M.D., TOSHIHIRO HABA, M.D., TOMIO KAMETANI, M.D., SEIGO ITO, M.D., JUNJI KOIZUMI, M.D., MASAYUKI OHTA, M.D., SUSUMU MIYAMOTO, M.D., AKIRA NAKAYAMA, M.D., HONIN KANAYA, M.D., HISANORI OIWAKE, M.D., AKIRA GENDA, M.D., AND RYOYU TAKEDA, M.D.

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 chylomycrons, 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.1,8,9,6

The relationship between VLDL and CAD has been less well defined.9,10 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.6 IDL and cholesterol-rich VLDL accumulate in abnormally high concentrations in the plasma of patients with type III hyperlipoproteinemia (broad b 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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