Pause-Dependent Torsade de Pointes Following Acute Myocardial Infarction
A Variant of the Acquired Long QT Syndrome

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OBJECTIVES
We report on a previously unrecognized form of the long QT syndrome (QT interval prolongation and pause-dependent polymorphic ventricular tachycardia [VT]) entirely related to myocardial infarction (MI).

BACKGROUND
Polymorphic VT in the setting of acute MI generally occurs during the hyperacute phase, is related to ischemia, and is not associated with QT prolongation. Although QT prolongation after MI is well described, typical pause-dependent polymorphic VT (torsade de pointes) secondary to uncomplicated MI was previously unknown.

METHODS
Of 434 consecutive admissions for acute MI, 8 patients had progressive QT prolongation that led to typical torsade de pointes. None of these patients had active ischemia or other known causes of QT prolongation. These patients were compared with 100 consecutive patients with uncomplicated MI who served as controls.

RESULTS
The incidence of torsade de pointes following MI was 1.8% (95% confidence interval 0.8% to 3.6%). The QTc intervals of patients and controls were similar on admission. The QTc lengthened by day 2 in both groups, but more so in patients with torsade de pointes (from 470 ± 6 to 46 to 492 ± 57 ms [p < 0.05] and from 445 ± 6 to 558 ± 84 ms, respectively [p < 0.01]). Maximal QT prolongation and torsade de pointes occurred 3 to 11 days after infarction. Therapy included defibrillation, magnesium, lidocaine and beta-blockers. Three patients required rapid cardiac pacing. The long-term course was uneventful.

CONCLUSIONS
Infarct-related torsade de pointes is uncommon but potentially lethal. An acquired long QT syndrome should be considered in patients recovering from MI who experience polymorphic VT as specific therapeutic measures are mandatory. (J Am Coll Cardiol 2001;38:1168–74) © 2001 by the American College of Cardiology

Torsade de pointes is a polymorphic ventricular tachycardia (VT) associated with a long QT syndrome (LQTS) (1). In its most typical form, sudden slowing of heart rate (i.e., pauses) invariably preceed each burst of torsade de pointes, and the recurrent arrhythmia is referred to as “pause-dependent torsade de pointes” (2–4). The long QT reflects a delay in myocardial repolarization caused by malfunctioning ion channels. This ion-channel malfunction may be due to mutations in the genes that encode these channels (in the congenital LQTS) or may be caused by medications, metabolic abnormalities, sympathetic imbalance, or bradyarrhythmias (in the acquired LQTS) (1).

We describe typical pause-dependent torsade de pointes following excessive QT prolongation in patients recovering from an otherwise uncomplicated myocardial infarction (MI). The QT prolongation after MI is a well-described phenomenon that adversely affects prognosis (5,6). However, to the best of our knowledge, this is the first series describing a LQTS (i.e., QT prolongation and torsade de pointes) related solely to MI.

METHODS
From May 1999 to May 2000, a total of 434 patients were hospitalized in our intensive cardiac care unit with acute MI. Eight (1.8% [95% confidence interval 0.8% to 3.6%]) of these cases were prospectively diagnosed as infarct-related LQTS because all the following criteria were met: 1) an acute MI was diagnosed clinically and was confirmed by serial electrocardiograms (ECGs) (showing new ST-segment deviation or new Q-waves) and by serial blood tests (showing high creatine kinase and creatine kinase-MB fraction or troponin-I levels); 2) spontaneous pause-dependent torsade de pointes (1–4) was documented during obvious QT prolongation (Fig. 1); 3) other causes of the LQTS (including medications known to affect repolarization, bradyarrhythmias, or metabolic abnormalities) (1) were excluded or considered highly unlikely (see the following text); and 4) a congenital LQTS was also considered unlikely because of the age at presentation and the medical history.

One hundred consecutive patients hospitalized in 1999 with MI (who were in sinus rhythm, had no bundle branch block and were not receiving drugs that prolong repolarization) were retrospectively included as a control group. The following ECGs were analyzed: 1) the admission ECG (generally during the hyperacute phase of infarction); 2) the
first ECG showing resolution of the acute ST changes (within 24 to 48 h of admission); 3) the trace showing maximal QT prolongation; and 4) the discharge ECG. All ECGs were recorded using standard gain (10 mm/mV) and speed (25 mm/s). The QT interval was defined as the interval between the onset of the QRS and the end of the T wave (defined as the return of the T wave to the baseline or the nadir between the T wave and the U wave when these were separated). The QT interval was measured in all 12 leads and analysis was done both for the longest QT and for the average QT of all the 12 leads. The QT values were "corrected for heart rate" using the Bazett formula \[QTc = QT/(RR)^{1/2}\].

Statistical analysis. All variables are expressed as mean ± SD. Time-related changes in QTc were analyzed by either one- or two-way analysis of variance for repeated measures, using the Newman–Keuls test for multiple comparisons. All analyses were done using GB-Stat software, version 6.5 (Dynamic Microsystems, Silver Springs, Maryland).

RESULTS

Study population. Eight patients (4 men, 4 women) aged 73 ± 13 years (range 47 to 88 years) developed marked QT prolongation and torsade de pointes following an MI (Q-wave anterior MI in 4 patients, inferior MI in 2 patients and non–Q-wave infarction in 2 patients). Their left ventricular ejection fraction was 42 ± 11% (range 28% to 56%). One of these patients had a previous infarction and two had previous coronary bypass surgery, including one with peri-operative infarction. All had hypertension, and one patient had asthma and diabetes. Only one patient (a 71-year-old woman) reported a previous syncopal episode (at the age of 69 years) and none had a familial history of sudden death, syncope or LQTS. Treatment on admission included thrombolytic therapy in two patients and primary angioplasty in one.

The control group included 100 patients (76% men), aged 62 ± 12 years, with Q-wave infarction in 78% (half of them in the anterior wall). Acute reperfusion therapy was given to 44% of patients. Their left ventricular ejection fraction was 0.56 ± 0.16. Both groups ("patients" and

Figure 1. Electrocardiogram (leads V1 through V6) of an 82-year-old woman who developed torsade de pointes three days after anterior myocardial infarction. The QT is normal on admission (QTc = 418 ms), increases by day 2 (QTc = 598 ms), reaches a maximal duration on day 3 (QTc = 645 ms) and normalizes by day 10 (QTc = 430 ms).
Developed torsade de pointes: *p

In the controls by day 2 but notably more so in patients who eventually.

The QTc significantly increased.

Longest QT during days 3 to 10 (controls).

The QTc at the time of hospital discharge (days 8 to 19). The QTc significantly increased.

In the controls by day 2 but notably more so in patients who eventually.

Derived from the mean QT of all the 12 leads gave similar differences.

Days 3 to 10: QTc recorded during the day of torsade de pointes (patient group) or in the trace showing the.

Prolongation of QT following MI.

The QTc of patients.

The QTc values.

The QTc subsequently shortened in the control group but continued to lengthen.

Torsade de pointes following MI.

The maximal QT.

At the time of maximal QT prolongation and recurrent ventricular fibrillation (VF) (one week later) prompted catheterization again.

Coronary anatomy.

Five patients underwent coronary angiography and all but one had single-vessel disease. Three of them had catheterization twice: before and after QT prolongation. The first patient (Fig. 3) had subtotal occlusion of a small diagonal branch in the initial catheterization and this was treated conservatively. He had the same findings when QT prolongation and recurrent ventricular fibrillation.

Acute and long-term therapy.

Four patients required direct current shock for terminating torsade de pointes that deteriorated to VF. In addition, treatment of torsade de pointes included intravenous magnesium (7 patients), lidocaine (6 patients) and incremental dosages of beta-blockers (in all but the patient with asthma). Nevertheless, three patients required emergency transvenous cardiac pacing for recurrent drug-refractory torsade de pointes, including two patients with recurrent VF. The QT interval spontaneously

Figure 2. QTc values (according to the longest QT of all 12 leads) in patients with torsade de pointes following myocardial infarction (black bars) and controls with uncomplicated myocardial infarction (white bars).

**Prolongation of QT following MI.** The QTc of patients and controls was similar on the day of admission for MI (Fig. 2). The QTc lengthened significantly by day 2 in both groups, but far more in patients with torsade de pointes (from 470 ± 46 to 492 ± 57 ms in the control group [p < 0.05] and from 445 ± 58 to 558 ± 84 ms in patients with torsade de pointes [p < 0.01]). The QTc values.

“Controls”) were similar in terms of gender, age, and left ventricular ejection fraction.

**Prolongation of QT following MI.** The QTc of patients and controls was similar on the day of admission for MI (Fig. 2). The QTc lengthened significantly by day 2 in both groups, but far more in patients with torsade de pointes (from 470 ± 46 to 492 ± 57 ms in the control group [p < 0.05] and from 445 ± 58 to 558 ± 84 ms in patients with torsade de pointes [p < 0.01]). The QTc values.

Torsade de pointes following MI. The maximal QT prolongation and QT-related arrhythmias occurred 3 days.

After torsade de pointes documentation. In one of them, angioplasty of an occluded right coronary artery had no noticeable effects on the prolonged QT. The second patient had an occluded right coronary artery with good collateral flow and was treated conservatively.

**Mode of onset.** At the time of maximal QT prolongation and torsade de pointes, all patients had stable, deep, inverted T-waves (Figs. 1, 3 and 4). All the arrhythmias evolved from sinus rhythm (rate 72 ± 8 beats/min). All episodes of torsade de pointes (>2 arrhythmias/patient) were pause-dependent. The pauses triggering the arrhythmias were postextrasystolic pauses (Figs. 3 and 4). These pauses lasted 1,170 ± 200 ms. The coupling interval of the extrasystole initiating torsade de pointes was 514 ± 120 ms.

Acute and long-term therapy. Four patients required direct current shock for terminating torsade de pointes that deteriorated to VF. In addition, treatment of torsade de pointes included intravenous magnesium (7 patients), lidocaine (6 patients) and incremental dosages of beta-blockers (in all but the patient with asthma). Nevertheless, three patients required emergency transvenous cardiac pacing for recurrent drug-refractory torsade de pointes, including two patients with recurrent VF. The QT interval spontaneously
shortened within 10 days of the MI in three of the patients with torsade de pointes (Fig. 1). These patients were discharged on a drug regimen that included beta-blockers and were instructed to avoid all medications that prolong repolarization. In the remaining patients, the QT was still prolonged at the time of the scheduled hospital discharge. These patients underwent implantation of a dual-chamber pacemaker (2 patients) or defibrillator (2 patients) equipped with a pause-prevention pacing algorithm (7). Device programming included features to prevent torsade de pointes as described elsewhere (7). Amiodarone was later prescribed to one patient with an implanted pacemaker because of frequent episodes of atrial fibrillation.

All the eight patients remained asymptomatic during a mean follow-up period of 16 ± 5 months. Repeated Holter recordings and periodic interrogation of the implanted devices failed to reveal any arrhythmias after hospital discharge. The QTc interval recorded three months after hospital discharge was <450 ms in all but the two patients treated with amiodarone.

DISCUSSION

Polymorphic ventricular arrhythmias (polymorphic VT [8] and VF [9]) related to an acute MI generally strike during the hyperacute phase, are clearly related to ischemia and are not associated with a long QT (8,10). In contrast, we describe polymorphic VT during the “healing phase” of MI in patients with no evidence of ongoing ischemia and following excessive QT prolongation. The marked changes in the QT morphology noted after pauses (Fig. 4), the long coupling interval of the extrasystoles triggering torsade de pointes, and the mode of onset of the arrhythmias (following a “short-long-short” sequence [Figs. 3 and 4]) support the diagnosis of “pause-dependent torsade de pointes due to a LQTS” in our patients. In the absence of identifiable causes of LQTS, we propose the term “infarct-related LQTS” to describe this phenomenon.

Main findings. In this case-control study, the QT interval generally increased during the course of an MI (Fig. 2). In agreement with previous studies (11–13), the QT prolongation was significant but transient, reaching a maximal level within days of an MI and shortening to the initial values by the 10th day in most patients. During this transient QT prolongation, however, eight patients developed all the features characteristic of a LQTS. These patients had QT intervals that were similar to those of the control group on admission but prolonged excessively afterwards. Although these giant QT intervals eventually normalized, malignant arrhythmias typical of torsade de pointes occurred 3 to 10 days after the infarction.

We cannot rule out a role for ischemia in the genesis of the arrhythmias observed. However, patients with multiple episodes of torsade de pointes had no clinical, ECG or angiographic findings to suggest that either acute ischemia or reinfarction was responsible for these particular arrhythmias. In fact, early appearance of deeply inverted, large T-waves has been correlated with effective reperfusion (14–16). Moreover, the similarities between the arrhythmias recorded in our patients and those reported in other forms of the LQTS (2–4) suggest a similar underlying mechanism not necessarily related to acute ischemia (see the following text).
Probable mechanism of infarct-related LQTS. In any LQTS (congenital or acquired), arrhythmias occur because: First, prolongation of the action potential affects voltage-dependent calcium-channels, causing a surplus of positive ions that creates early after depolarizations (EADs). Eventually, these EADs reach threshold amplitude and trigger ventricular extrasystoles (1). Second, cells in the mid-myocardium, with electrophysiologic properties similar to Purkinje fibers, display longer action potentials and more EADs than epicardial or endocardial cells (17). The result-ant heterogeneity of repolarization allows the propagation of multiple waves of reentry responsible for torsade de pointes (18).

Similar conditions may develop during the healing phases of an MI: 1) The action potential of Purkinje fibers (which initially shortens during prolonged ischemia) not only normalizes during a recovery period, but also increases over a control value (19). This action-potential prolongation often leads to EADs and to triggered arrhythmias in infarct models (19). 2) The difference in the refractory period between adjacent areas in the ventricle is maximal a few days after an MI and normalizes within weeks (20). According to these experiments, the odds for torsade de pointes should be maximal within days of an infarct, as observed in our patients. Third, as in other forms of LQTS (2,4), torsade de pointes after MI was preceded by “short-long-short” cycles. Such oscillations in cycle length may potentiate calcium-loading (21) (triggering further extrasystoles), while increasing the dispersion of repolarization by predominantly increasing the action potential in ischemic myocardium (facilitating re-entry) (22).

Rather than originating from the infarcted zone, QT prolongation could be related to a compensatory hypertrophy (remodeling) of noninfarcted zones in the left ventricle. After all, action-potential prolongation in hypertrophic myocytes is a universal consequence of hypertrophy, regardless of its cause (23). In a rat model of MI, down-regulation of potassium channel gene expression and potassium currents (with consequent action potential prolongation and EADs) occurs in noninfarcted zones of the left ventricle as early as three days after MI, long before the morphologic changes of hypertrophy can be identified (24). The striking T-wave changes seen in our patients also deserve comment. Very recent data (25) suggest that such giant and bizarre T-wave changes may result from combined blockade of both IKr and Iks currents. Interestingly, reduction of the messenger RNA (mRNA) levels—and consequently, of the channel subunits that form IKr and Iks channels—can
occur in the layer of epicardium surviving around an endocardial infarcted zone (26). Alternatively, the patchy sympathetic denervation that often follows MI (27) could have contributed to the QT prolongation and arrhythmogenesis in our patients (28). This could explain why the QT morphology (with giant inverted T-waves) in our patients is similar to that observed when unilateral nervous system disease (29) or pathologies causing “sympathetic imbalance” (1,30) are the basis of an acquired LQTS.

**Previous studies.** Ischemic polymorphic VT, which has been the focus of previous studies (8,31,32), differs from infarct-related torsade de pointes in terms of pathophysiology and ECG manifestations. During ischemia, the excessive dispersion of repolarization is due to uneven shortening of the action potential in different myocardial layers (33). This enables reentrant arrhythmias during the very early phases of repolarization. Consequently, “ischemic polymorphic VT” is triggered by extrasystoles with very short coupling interval (the “R-on-T” phenomenon) and is not pause-dependent (8,10). Some investigators have used the term “torsade de pointes” to describe polymorphic arrhythmias during MI (31,34). However, the available illustrations suggest that the majority of the patients in these studies had (short QT) “ischemic polymorphic VT.”

**Study limitations.** First, documentation of torsade de pointes was required for inclusion in our series. However, it is possible that short asymptomatic arrhythmias were missed in additional patients because torsade de pointes tends to occur when ECG monitoring is less rigorous (>48 h after hospitalization). Thus, it is possible that we underestimated the incidence of infarct-related LQTS. Second, amiodarone could have contributed to the arrhythmia in one patient. Moreover, the list of nonantiarrhythmic drugs that prolong repolarization (by means of potassium-channel blockade) keeps expanding (35), and it is possible that drugs that are now considered safe and were received by our patients will prove to be potassium-channel blockers in the future. Third, a congenital LQTS would be an unlikely explanation for the QT prolongation in our patients with MI. This enables reentrant arrhythmias during the very early phases of repolarization. Consequently, “ischemic polymorphic VT” is triggered by extrasystoles with very short coupling interval (the “R-on-T” phenomenon) and is not pause-dependent (8,10). Some investigators have used the term “torsade de pointes” to describe polymorphic arrhythmias during MI (31,34). However, the available illustrations suggest that the majority of the patients in these studies had (short QT) “ischemic polymorphic VT.”

**Clinical implications.** QT prolongation after infarction is common (6,11–13), whereas infarct-related LQTS is rare, yet potentially lethal. Careful monitoring of patients in whom the QT interval fails to shorten prior to hospital discharge is probably wise. Detection of “warning signs” for torsade de pointes, like postextrasystolic QT changes (1,3), should call for further caution. It is important to recognize this syndrome of “postinfarction LQTS” as this form of “late VF” (occurring >48 h after MI) may not necessarily require implantation of an automatic defibrillator. Although it is impossible to assess the contribution of long-term cardiac pacing to the noneventful course in our patients, their benign long-term course is reassuring.

**REFERENCES**