Electrophysiology, Pacing, and Arrhythmia

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A Practical Approach to Torsade de Pointes

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Summary: The term torsade de pointes refers to polymorphic ventricular tachycardia that occurs in the setting of an abnormally long QT interval. While the most common cause is treatment with QT prolonging drugs, torsade de pointes also occurs in the congenital long QT syndromes and in the setting of acquired heart block or severe electrolyte disturbance, notably hypokalemia. Among QT prolonging drugs that cause torsade de pointes, both antiarrhythmics and "noncardioactive" drugs have been recognized. The electrocardiographic features of torsade de pointes include labile QT intervals, prominent U waves, and a "pause-dependent" onset of the arrhythmia. Treatment consists of recognition of the syndrome, correction of underlying electrolyte abnormalities, and withdrawal of any offending drugs. Magnesium, isoproterenol, or cardiac pacing provides specific antiarrhythmic therapy in torsade de pointes.

Key words: long QT syndrome, torsade de pointes, proarrhythmia

History

The syndrome of syncope occurring shortly after initiation of quinidine therapy was recognized as early as the 1920s,[1] but the underlying mechanism was not defined until the 1950s and 1960s. In the 1950s, a relationship between marked prolongation of the QT interval and sudden death was described in a number of families, with or without deafness.[2-4] However, it was only in the 1960s that the association between QT prolongation and a specific arrhythmia was recognized. In 1964, Seltzer and Wray[5] reported that quinidine syncope was due to an arrhythmia they termed "paroxysmal ventricular fibrillation" and which we would now call polymorphic ventricular tachycardia. It is interesting that, in the examples presented, marked pause-dependent prolongation of QT interval was present, but was not commented upon. In 1966, Dessertenne, a French cardiologist, reported that syncope in an elderly patient with heart block, for whom he was caring, was actually due to bradycardia-dependent polymorphic ventricular tachycardia and not to advanced degrees of heart block.[6] Dessertenne recognized that the tachycardia had a particular pattern, with each beat changing its axis slightly from the preceding one; this gave prolonged episodes a distinctive morphologic appearance that he termed "torsade de pointes." In retrospect, the first published episode of torsade de pointes was probably in 1935, in association with hypomagnesemia.[7]

Causes of Torsade de Pointes

It is important to recognize that the term torsade de pointes implies a polymorphic ventricular tachycardia occurring in the setting of an abnormally long QT interval. Polymorphic ventricular tachycardia occurring in the absence of any QT prolongation does occur (Fig. 1), but has different clinical features and responds to quite different therapeutic approaches.[8, 9] The most common cause for torsade de pointes is administration of drugs that prolong the QT interval (Table I). This includes not only antiarrhythmic drugs but also a wide range of drugs not generally thought to have important cardiovascular effects. As discussed below, the incidence of torsade de pointes during drug therapy generally increases at higher dosages and/or plasma concentrations; it is widely recognized that quinidine is an exception, with torsade de pointes occasionally occurring with single doses at subtherapeutic plasma concentrations.[10-12] Not every case of torsade de pointes is related to drug therapy. Aside from cases of the congenital long QT syndrome, occa-

Polymophic VT/short QT:
* Short QT
* No pause dependence
* Very rapid

(A)

Torsade de pointes:
* Long QT
* Pause-dependent
* Slower, more organized
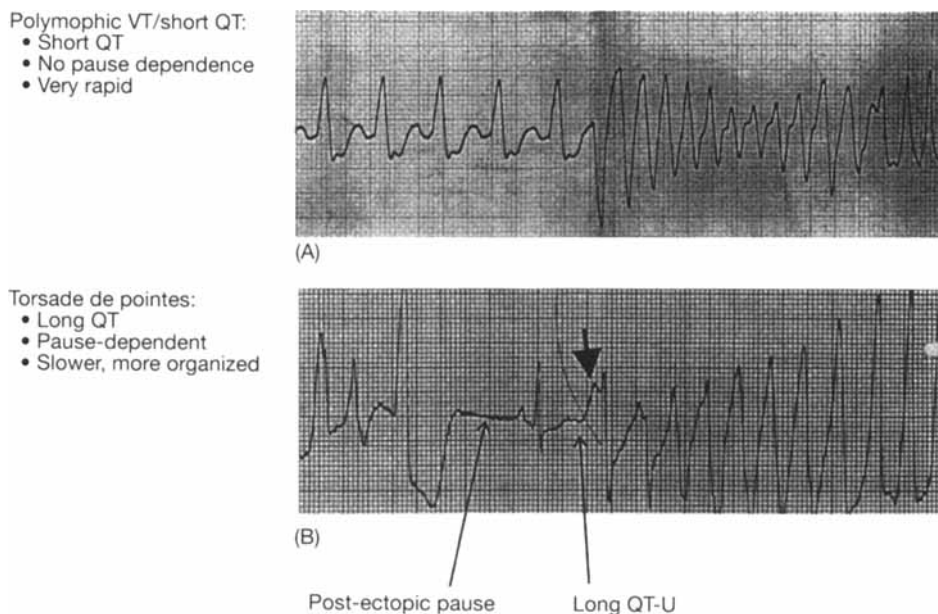
(B)

Post-ectopic pause   Long QT-U

FIG. 1   Contrasting electrocardiographic features of polymorphic ventricular tachycardia with a short QT interval (A) and torsade de pointes (B). The onset of a typical episode of torsade de pointes is shown: the sinus beat that follows a post-ectopic pause is characterized by marked QT-U interval prolongation. The coupling between the last sinus beat and the first beat of the tachycardia is long and occurs typically after the peak of the QTU complex which, in this lead, consists of a prominent U wave (heavy arrow). The tachycardia shown in (A) is also polymorphic, but lacks the pause-dependent features of torsade de pointes; rather, its onset does not follow a pause and is short-coupled.

sional patients with advanced hypokalemia or hypomagnesemia or patients with heart block (as in Dessertenne's index case) can present with torsade de pointes. Other causes of QT prolongation, such as hypocalcemia or hypothyroidism, are very rare causes of torsade de pointes. Similarly, marked QT interval prolongation can occur in some patients with acute central nervous system lesions such as stroke, but torsade de pointes seems to be relatively rare.

Normal QT Intervals

The QT interval on the surface electrocardiogram (ECG) reflects the duration of action potentials in individual cardiac cells. Action potential duration, in turn, is determined by the balance between inward and outward currents flowing across the cell membrane during systole. Congenital lesions, drugs, or other factors that upset this balance can prolong cardiac action potentials, and hence the QT interval. For example, it is now known that patients with the congenital long QT syndrome harbor mutations in genes encoding ion channels, the structures through which ion currents flow. Multiple mutations causing the syndrome have been described in different families.[13] In some, QT prolongation is attributable to a defect in sodium channels, allowing increased inward current;[14, 15] in others, defects that reduce the amplitude of outward currents are responsible.[16, 17] One such outward current is termed I_{Kr}; I_{Kr} is also blocked by many drugs that cause torsade de pointes,[18, 19] thereby explaining the similar clinical features of

the congenital and drug-acquired syndromes. Similarly, hypokalemia probably prolongs the QT interval by decreasing I_{Kr}.[19, 20]

The normal QT interval is dependent on rate in two ways. First, the QT interval is normally longer at slower "steady-state" rates. Second, the QT interval is normally prolonged when the rate abruptly slows, as, for example, after post-ectopic pause. If the QT interval for a single heart beat is measured in all 12 leads of the ECG simultaneously, a range of values is obtained; the difference between the longest and shortest value, which some have termed "dispersion of repolarization" and which is thought to represent regional differences in action potential duration, can be up to 50 ms.[21, 22] Measurement of QT interval duration and QT dispersion is often confounded by the development of U waves. A general rule of thumb is that if U waves are very small, they should not be considered in the measurement of the QT interval, whereas if they are large (e.g., >25–50% of the height of the T wave), the measurement of the QT interval duration should include the U wave. U waves are presumed to represent regions of the ventricle that repolarize late compared with other regions; cells in the mid-myocardium may be the source of U waves.[23]

Electrocardiographic Characteristics of Torsade de Pointes

QT interval control is abnormal in patients with torsade de pointes: steady-state QT intervals are prolonged; QT intervals

TABLE 1 Drug-associated torsade de pointes

Antiarrhythmics
  Quinidine
  Disopyramide
  Procainamide (NAPA)
  Sotalol
  Ibutilide
  Amiodarone (rare)
  Some investigational agents
Calcium-channel blockers
  Bepridil
  Lidoflazine
Non-antiarrhythmics
  CNS-active agents
    Thioridazine
    Tricyclic antidepressants
    Pimozide
  Antibiotics
    Erythromycin
    Pentamidine
    Trimethoprim-sulfa
  Antihistamines
    Terfenadine
    Astemizole
  Miscellaneous
    Terodiline
    Liquid protein diets
    Organophosphorus insecticide poisoning
    Ketanserin
    Cisapride
    Probucol

display marked increases in duration and changes in morphology after a pause; and QT "dispersion" is increased, often to >120 ms. Most episodes of torsade de pointes occur in a "pause-dependent" fashion;[11, 12, 24] that is, after an ectopic beat or run of tachycardia, a normal post-ectopic pause is followed by a supraventricular (usually sinus) beat (Fig. 1). The QTU complex of this supraventricular beat is very long and frequently shows very large U waves. The arrhythmia typically starts after the peak of the U wave. Some have reported that the heart rate seems to increase in the minutes prior to an episode of torsade de pointes, suggesting underlying sympathetic activation.[25] When the onset of torsade de pointes is recorded in many leads simultaneously, it is not unusual to see pause-dependent prolongation of the QT interval in some leads, whereas in other leads the QT interval appears normal and there is a very prominent U wave.[26] In general, episodes should be at least 5 to 10 beats long before the term torsade de pointes is applied, since the polymorphic nature of the tachycardia may not be readily appreciated with shorter episodes. During episodes of torsade de pointes, it is not unusual to observe what appears to be monomorphic ventricular tachycardia, especially if the arrhythmia is monitored only in a single lead and for brief periods of time. Frequent single premature ventricular contrac-

tions (PVCs) occurring after the peak of a very prolonged QTU complex are also common in patients who subsequently go on to develop torsade de pointes; it seems likely that these PVCs arise from the same mechanism(s) as those determining the longer episodes. Most recorded episodes of torsade de pointes are self-limited (and associated either with no symptoms or with syncope), although occasional episodes degenerating to ventricular fibrillation can occur. Presumably it is this transition to ventricular fibrillation that accounts for deaths in patients with congenital long QT syndrome as well as, possibly, some deaths in patients receiving QT-prolonging drugs.

Patients who develop torsade de pointes display substantial lability in QT interval, not only in space ("dispersion of repolarization") but also in time; that is, QT intervals can be only modestly prolonged at one instant and seconds later become markedly prolonged. QT alternans is an extreme example of this lability and is most frequently seen in patients with the congenital forms of the syndrome. This lability in the QT interval makes it difficult to establish firm ground rules as to how long a QT interval the clinician should tolerate during treatment with a QT-prolonging drug. While schemes to rate-correct the QT interval are commonly used,[27] it is probably the absolute duration of the QT interval and not the rate-corrected QT interval that determines risk for torsade de pointes. For example, QT intervals of 389 ms at a heart rate of 120 beats/min and of 674 ms at a heart rate of 40 beats/min both give a rate-corrected QT interval of 550 ms; it is the patient with the heart rate of 40 beats/min who is probably at greater risk. Furthermore, QT interval corrections are based on measurements with a constant underlying rate and so do not take into account QT interval prolongation that is seen after a pause. Thus, the duration and morphology (e.g., a large U wave) of a postpause QT interval probably provide more important clues to the development of torsade de pointes than does mere rate-correction of the QT interval.

Can Patients at Risk for Torsade de Pointes Be Identified?

With an increasing awareness of the phenomenon of drug-induced torsade de pointes has come a delineation of at least some factors that appear to confer increased risk for this arrhythmia. Most authorities would limit QT interval prolongation to <520 (or perhaps 550) ms in patients receiving a QT-prolonging drug. Exceptions include some patients with bundle-branch block (in whom the QT interval may be >600 ms even prior to the initiation of drug therapy) and patients receiving amiodarone, in whom the risk for torsade de pointes appears considerably smaller than that with other QT-prolonging drugs.[28, 29] It is well recognized that QT intervals are longer in women than in men, although the mechanisms are not well understood. It is interesting, therefore, that in virtually all series of torsade de pointes there is a 2–3 fold higher incidence of the arrhythmia among women.[30] This includes not only drug-associated cases but also extends to the congenital long QT syndromes, in which syncope is more common among women

who carry long QT mutations than among men who carry mutations.[31]

In most series, hypokalemia and hypomagnesemia are common among patients who develop drug-induced torsade de pointes. It is not well established whether the type of underlying heart disease affects the incidence of torsade de pointes, although there is some suspicion that left ventricular hypertrophy or congestive heart failure may increase the risk. Among patients with atrial fibrillation treated with QT prolonging drugs, torsade de pointes most frequently develops shortly after conversion to normal rhythm.[32] Whether this is a function of the decrease in rate that often accompanies cardioversion or whether it is a manifestation of some complex effect of antecedent rapid rates on the subsequent development of torsade de pointes remains uncertain.

It has long been recognized that torsade de pointes during quinidine therapy can occur at subtherapeutic dosages and concentrations.[11, 12] In contrast, the incidence of torsade de pointes is dose-dependent (and presumably concentration-dependent) in the case of sotalol;[33] it is important in this regard to recall that high sotalol concentrations can develop even at normal doses in patients with renal failure.[34] Similarly, torsade de pointes developing during procainamide therapy is often due to accumulation of the active metabolite NAPA, often to concentrations of >20–30 µg/ml, in patients with renal failure.[35] Among patients with ventricular tachycardia treated with sotalol at dosages ≥480 mg/day, the incidence of torsade de pointes was 4–5%. Among patients treated with quinidine or sotalol for atrial fibrillation, incidence rates seem to be in approximately the same range, 2–10% depending on the series. The incidence of torsade de pointes during oral amiodarone therapy is probably under 1%, although the arrhythmia can occur when other risk factors such as hypokalemia are present. The incidence of torsade de pointes during treatment with other antiarrhythmics has not been estimated, but it is probably similar to that with quinidine or sotalol. When intravenous ibutilide is used for acute conversion of atrial fibrillation or flutter, the incidence of torsade de pointes varies from 1–8%, depending on the series and the underlying rhythm; in the ibutilide experience, torsade de pointes was more common among patients treated for atrial flutter than among those treated for atrial fibrillation.[36,37]

The development of torsade de pointes during treatment with the "noncardiac" drugs listed in Table I appears to depend on either high dosages or attainment of high plasma concentrations. The mechanisms underlying torsade de pointes occurring with terfenadine therapy have been the best studied,[38] although cases during astemizole or cisapride therapy likely arise from the same etiology. Terfenadine itself is a QT-prolonging (I_{Kr} blocking) compound,[38–40] while its acid metabolite, which is an antihistamine, has no electrophysiologic actions. In most individuals, terfenadine is rapidly biotransformed to its acid metabolite prior to reaching the systemic circulation. When this metabolic pathway is blocked or saturated, terfenadine itself accumulates in plasma and torsade de pointes results. Saturation of metabolism occurs with overdose, while block of metabolism occurs with advanced liver disease or

with drugs that inhibit the specific enzyme responsible for the biotransformation of terfenadine to its metabolite. These inhibitors include erythromycin and other macrolide antibiotics, ketaconazole and other azole antifungals, and (possibly) some calcium-channel blockers. The noncardioactive acid metabolite of terfenadine, fexafenadine, has now been marketed as an antihistamine.

Animal data strongly suggest that the risk of torsade de pointes during administration of an intravenous QT-prolonging drug may be increased by increasing the rate of infusion.[41] Thus, clinicians using ibutilide should not administer the drug any more rapidly than the 1 mg over 10 min recommended by the manufacturer.

The Treatment of Torsade de Pointes

The most important principle in the treatment of torsade de pointes is to recognize the arrhythmia. All QT-prolonging drugs should be withdrawn, and even modest hypokalemia should be corrected. In vitro studies suggest that potassium will not only shorten the QT interval but may also decrease the potency of QT-prolonging drugs;[19] thus, serum potassium should be kept in the high normal range. Long episodes of torsade de pointes should be treated with cardioversion.

In vitro studies have delineated electrophysiologic abnormalities—early afterdepolarizations (EADs) and triggered activity—that are likely responsible for the initiation of torsade de pointes.[42, 43] EADs are abnormalities in the terminal phase of the action potential that probably contribute to the development of U waves on the surface ECG. Triggered activity consists of spontaneous depolarization(s) arising from EADs; these probably account for initiation of torsade de pointes itself. Based on these in vitro electrophysiologic abnormalities, two general approaches to therapy in torsade de pointes have been described:

(1) Shorten the action potential: This will prevent both EADs and triggered activity. The most effective way of shortening the action potential is cardiac pacing. Pacing not only shortens the action potential and QT, but prevents long postectopic pauses that almost invariably precede the development of episodes of torsade de pointes. Generally, pacing at a heart rate of 90–100/min is sufficient. Isoproterenol, usually at a dose of 1–4 µg/min (sufficient to raise the heart rate to 90–100/min), can also be effective.

(2) Eliminate triggered activity: Interventions that eliminate triggered activity in vitro are predicted to eliminate episodes of torsade de pointes without necessarily shortening the QT interval. Magnesium and beta blockers probably act by this mechanism. Intravenous administration of 1–2 g magnesium sulfate appears to prevent recurrences of torsade de pointes in most patients (although placebo-controlled trials have obviously not been done).[44] It is interesting that while magnesium prevents episodes of torsade de pointes, it does not shorten the QT interval. Similarly, beta blockers seem to be quite effective in preventing recurrent episodes of syncope among patients with congenital long QT syndromes,[45] again without normalizing QT. A number of other therapies have

been tried in patients who have arrhythmia recurrences despite these standard therapeutic approaches. These include calcium-channel blockers, alpha blockers, potassium channel openers, lidocaine, and mexiletine; while there is an in vitro rationale for each of these approaches, convincing clinical data that they are effective have not yet been developed.

The Future

The recognition of a distinct clinical syndrome, torsade de pointes, has led to delineation of a set of factors that helps the clinician to identify the patient at risk. It is important that the description of these clinical factors has also helped unravel the basic mechanisms underlying the arrhythmia, making it possible to identify effective therapies. Most recently, molecular defects responsible for the congenital and drug-induced forms of long QT-related arrhythmias have begun to be unraveled. This information may not only help provide the clinician with further guidance in the appropriate selection of patients, but may also help in the rational use of available drugs and the development of improved drug therapies that lack this adverse effect.

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