

Review Article

The prolonged QT interval – a frequently unrecognized abnormality

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Introduction

The clinical importance of the long QT interval syndrome lies in its association with malignant ventricular dysrhythmias which are usually amenable to treatment with either drugs or cardiac pacing.

The QT interval extends from the beginning of the QRS complex (whether the initial component is a Q or an R wave) to the end of the T wave. It therefore represents the algebraic sum of the individual action potentials of the ventricular myocytes, including both depolarization (the QRS complex or QJ interval) and repolarization (the T wave or JT interval). The rapid process of depolarization is rarely sufficiently prolonged to make any clinically significant difference to the QT interval duration and the term effectively refers to changes in the duration of repolarization, that is the JT interval.

Physiological variations in the QT interval

It is well known that the QT interval alters with heart rate (Bazett, 1920). However, heart rate is only one of the determinants of the QT interval duration (Rickards & Norman, 1981) and other factors, particularly changes in autonomic activity, also contribute to QT interval shortening during exercise (Browne *et al.*, 1983b). By comparing QT interval changes during atrial synchronized and asynchronous ventricular pacing, Fanazapazir *et al.* (1983) determined that the contribution of the intrinsic effect of the heart rate to QT interval shortening during exercise varied from 26 to 75%.

Sleep represents a naturally occurring period of increased parasympathetic tone or sympathetic tone withdrawal (Kleinman, 1963; Baust & Bohnert, 1969) and prolongs the QT interval independently of the

slowing heart rate (Browne *et al.*, 1983a; Lown *et al.*, 1973).

The physiological control of the QT interval has been used to construct a cardiac pacemaker which senses the interval between the delivered stimulus and the evoked T wave and uses this interval to set the subsequent pacemaker escape interval (Rickards & Norman, 1981; Donaldson *et al.*, 1983).

Measurement of the QT interval

Measurement of the QT interval on the surface electrocardiogram (ECG) can present technical problems because the end of the T wave may be difficult to define. The point at which the line of maximal downslope of the T wave crosses the baseline is therefore often used to identify the end of the T wave. The surface ECG leads chosen for QT interval measurement are those which show the greatest T wave amplitude and duration. The QT interval should be measured in at least three consecutive cardiac cycles and the time values averaged. Although tables that list normal values for a specific cardiac rate, age and sex are available, Bazett's formula (1920) for calculating the QT interval corrected for heart rate is commonly used:

$$QT \text{ calculated } (QT_c) = \frac{QT \text{ (measured)}}{k \sqrt{RR \text{ interval (s)}}}$$

where k is 0.37 for men and 0.40 for women. The upper limit is 0.39 s for men and 0.44 s for women (Braunwald, 1984). Because of variations in the measured QT interval as a result of influences other than heart rate, such as sympathetic and parasympathetic activity, drugs, electrolyte changes, ventricular hypertrophy, ischaemia, and acid-base disturbances, different ranges of normality are accepted by different investigators. For practical purposes therefore, minor deviations from the expected QT_c interval should be

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disregarded as being of questionable clinical significance.

The use of QT_c is at times misleading when interval changes are examined in association with rapid changes in heart rate (Camm *et al.*, 1984). The biophysical effect of heart rate on QT interval develops slowly (Arnold *et al.*, 1982) and therefore the use of formulae such as that described by Bazett may result in gross overcorrection (Milne *et al.*, 1980).

Repolarization, the vulnerable period and the long QT interval

Myocardial repolarization is complex, poorly understood and even more difficult to study than depolarization. It is also, possibly because of its slower time course, more obviously affected by disease, drugs, and biochemical abnormalities. It is normally a well coordinated but non-uniform process, as is evident from the consistent asymmetry of the normal T wave.

The vulnerable period is that part of the cardiac cycle during which ventricular tachycardia or fibrillation can be most easily provoked and this is always the relative refractory period of the ventricular myocardium, corresponding to the declining limb of the T wave from peak to iso-electric line. Increased vulnerability to the provocation of ventricular fibrillation can be induced by many means which have in common the effects of causing temporal dispersal of repolarization often combined with increased excitability. Temporal dispersal of the repolarization process may occur as a result of premature repolarization of some myocardial cells or as abnormally delayed repolarization of other cells. The latter may be reflected in the surface electrocardiogram as prolongation of T wave with corresponding lengthening of the QT interval.

Marked lengthening of the QT interval of the order which can be measured on the surface ECG is almost inevitably associated with increased temporal dispersal of repolarization and thus increases the duration of the vulnerable period as well as decreasing the threshold for ventricular fibrillation.

The severe prolongation of repolarization found in the long QT syndrome (LQTS) decreases the degree of prematurity required for an ectopic beat to occur within the vulnerable period and therefore enhances the likelihood of ventricular arrhythmias (Lipman *et al.*, 1979; Montro, 1981). These hypotheses account for the frequent association of arrhythmias and the prolonged QT syndrome. They may also explain why some patients with abnormally prolonged QT intervals run a trouble free course.

Conventional electrocardiography only reflects the net resultant of the repolarization of all ventricular myocardial cells. Thus any abnormal temporal disper-

sion of repolarization which involves premature repolarization will not be reflected by prolongation of the QT interval and, unless the mass of cells is large, may not even cause an alteration of T wave morphology. Such patients are, however, just as likely to be at risk from ventricular dysrhythmias as those in whom temporal dispersion of ventricular repolarization is the result of abnormally delayed repolarization (Han & Moe, 1964; Han & Goel, 1972; El-Sherif *et al.*, 1977). These concepts can explain the apparently paradoxical effects of different drugs. Thus, anti-arrhythmic agents which prolong repolarization may act by normalizing premature depolarization in abnormal myocardium, while in other situations, such as torsades de pointes in the acquired LQTS, drugs which shorten abnormally prolonged depolarization, such as isoprenaline, are effective when many standard agents are not or may even exacerbate the dysrhythmia (Bennett, 1982; Soffer *et al.*, 1982).

Long term treatment of rabbits with beta adrenergic antagonists induces several adaptive changes in the myocardium which persist long after the drugs have been eliminated from the body (Vaughan Williams, 1977). This 'adaptive syndrome' includes prolongation of the action potential duration and the QT interval and both these effects have been shown to occur in man although the full clinical implication of the findings are unclear (Edvaardsson & Olsson, 1981; Vaughan Williams *et al.*, 1980; Milne *et al.*, 1980).

Torsades de pointes

Torsades de pointes is virtually always associated with prolongation of the QT_c interval (Smith & Gallagher, 1980) and is the most important and singular arrhythmia complicating both acquired and congenital long QT interval syndromes (Bonatti *et al.*, 1983; Montro, 1981). Torsades de pointes is characterized by short intervals of ventricular tachycardia which consist of bursts of ventricular waves occurring at a high rate (from 150 to 250 beats/min) and showing progressively varying amplitude and polarity (Figure 1). Attacks may be brief or prolonged, when syncope may occur. Attacks most often stop spontaneously but on some occasions they progress to ventricular fibrillation and death (Krikler, 1976; Krikler *et al.*, 1976). The distinction between torsades de pointes and those polymorphous ventricular tachycardias occurring in patients with a normal QT interval has important therapeutic implications. The former requires strict avoidance of all drugs that may potentially further delay repolarization, including class 1 antiarrhythmic agents such as quinidine, disopyramide and lignocaine. Immediately, the initiation of cardiac pacing is often necessary for arrhythmia control and, on a long term basis, sym-

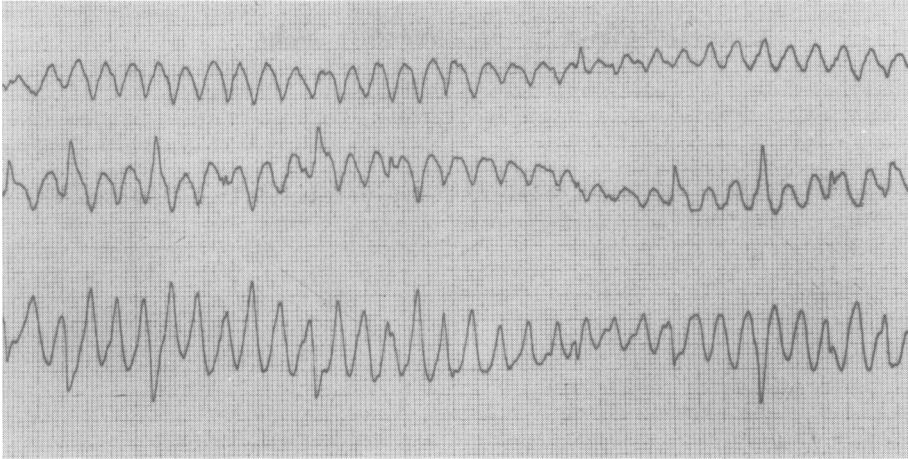


Figure 1 Torsades de pointes illustrating bursts of ventricular waves at a high rate with varying amplitude and polarity.

pathetic nervous blockade is beneficial. In contrast, polymorphous ventricular tachyarrhythmias with a normal QT interval respond to conventional therapy (Soffer *et al.*, 1982).

Congenital long QT syndrome

A prolonged QT interval may be due to congenital (idiopathic long QT syndrome) or acquired disease states. In 1957, Jervell and Lange-Nielson reported the congenital association of QT prolongation, syncope, sudden death and deafness. Six years later Romano *et al.* (1963) and Ward (1964) independently reported a similar syndrome in children with normal hearing. These conditions are collectively known as the long QT syndrome (LQTS) and are both familial; the variety reported by Jervell and Lange-Nielson is transmitted as an autosomal recessive while the Romano–Ward syndrome is inherited as an autosomal dominant (Fraser *et al.*, 1964; Ward, 1964). To date no positive association has been demonstrated with any particular HLA antigen and there is no evidence of viral aetiology (James *et al.*, 1978).

In the British Isles, the incidence of congenital LQTS is not less than one per 300,000 births and may be greater (Fraser *et al.*, 1964). A world wide prospective register was established in 1979. The average age of the population was 24 y with almost twice as many women as men. Congenital deafness was present in 6% of patients and all had one or more syncopal episodes before age 10 y (Schwartz *et al.*, 1983).

The LQTS is an idiopathic disorder in which the affected individuals have an unusual ventricular repolarization abnormality and a propensity to syncope and fatal ventricular tachyarrhythmias. The pathog-

nomonic electrocardiographic finding is an abnormal lengthening of the QT interval with asymmetric or notched T waves. The syncopal episodes are almost always induced by one or more of the following: (a) psychological or physical stress, (b) induction of anaesthesia (Callaghan *et al.*, 1977; Forbes & Morton, 1979; Medak & Bennmof, 1983) and (c) medications which prolong the QT interval or change the sympathetic tonal control of the heart (Reynolds & VanderArk, 1976; Puritz *et al.*, 1977; Siklos *et al.*, 1978; Laasko, 1981; Ludomirsky *et al.*, 1982). Patients may also develop brief episodes of deep, severe T wave inversion following the same stimuli which trigger syncopal attacks (Schwartz *et al.*, 1975).

Pathophysiology

The pathogenesis of congenital prolonged QT interval is still unclear, but the most popular hypothesis centres around the adrenergic nervous system – unbalanced activity of the cardiac sympathetic nerves which is either exaggerated on the left or depressed on the right (Schwartz *et al.*, 1975; Browne *et al.*, 1983a). This asymmetry of sympathetic stimulation results in severe prolongation (and temporal dispersal) of repolarization of the ventricular myocardium leading to increased susceptibility to fibrillation (Vaughan Williams, 1982).

Further evidence for involvement of the sympathetic nervous system lies in: (a) syncopal attacks which may be reproducibly precipitated by events or activities that increase sympathetic stimulation, such as emotion or physical exercise; (b) the production of characteristic electrocardiographic signs – QT interval prolongation and episodes of altered T wave activity – by asymmetric alterations in sympathetic tone (Sch-

wartz & Malliani, 1974); (c) satisfactory therapeutic results obtained by antagonizing the effects of sympathetic activity on the heart with beta adrenoceptor antagonists. Ablation of the left stellate ganglion and first thoracic ganglion ablation may also be successful (Schwartz *et al.*, 1975).

The results of animal studies also support the importance of unbalanced sympathetic stimulation in the genesis of the congenital LQTS (Schwartz & Malliani, 1974; Schwartz *et al.*, 1975).

Anaesthesia

The detection and management of long QT interval syndrome in patients undergoing surgery is of particular importance. Patients who have not been treated appropriately prior to general anaesthesia have all had severe ventricular arrhythmias or a cardiac arrest or both at some time in the perioperative period (Callaghan *et al.*, 1977; Forbes & Morton, 1979; Medak & Benumof, 1983; Owitz *et al.*, 1979; Wig *et al.*, 1979; Brown *et al.*, 1981; Ponte & Lund, 1981). This is hardly surprising in view of the intense sympathetic stimulation which occurs during induction of anaesthesia and intubation, perioperative haemodynamic stresses and the variations in autonomic tone occurring during recovery from anaesthesia.

Prognosis and treatment of congenital LQTS

In a retrospective series of 233 patients with LQTS, the 15 y survival after the first syncope was 45% in untreated patients and 90% in patients treated with propranolol or left stellate ganglionectomy (Schwartz *et al.*, 1983).

The evidence to date strongly suggests that any patient with prolonged QT interval syndrome should have a trial of long term beta adrenoceptor blockade. Propranolol, by antagonizing excessive sympathetic discharge, causes homogeneity of repolarization and shifts the rate adjusted QT interval closer to the normal range thereby reducing the frequency of arrhythmias and the death rate (Krikler, 1976). A linear dose response relationship may exist – the greater serum propranolol concentration being associated with a shorter QT interval (Medak & Bennumof, 1983). Percutaneous left stellate ganglion blockade also suppresses symptoms perioperatively (Moss & MacDonald, 1971; Callaghan *et al.*, 1977).

In patients in whom medical treatment achieves only a reduction in syncopal attacks, left sympathectomy suppresses attacks and shortens the QT interval (Schwartz *et al.*, 1975). Ventricular pacing may also be effective by 'normalizing' depolarization and subsequent repolarization (Keren *et al.*, 1981). Those patients who suffer from both paroxysmal ventricular fibrillation and paroxysmal complete heart block

usually require both long term beta blockade and permanent pacing.

In patients undergoing surgery and general anaesthesia adequate premedication should be given in addition to these measures to minimize the release of catecholamines and reduce sympathetic nervous system activation resulting from fear and anxiety. Halothane lowers the ventricular arrhythmia threshold produced by exogenously administered noradrenaline and is a particularly poor choice of anaesthetic agent (Wig *et al.*, 1979; Medak & Bennumof, 1983) but isoflurane, which raises the ventricular arrhythmia threshold is preferable (Joas & Stevens, 1971; Medak & Bennumof, 1983).

Acquired long QT syndrome

Apart from congenital syndromes, there are a number of drugs and clinical disorders associated with prolongation of the QT interval. In the present issue, Duncan & Ramsey (1985) have reported a case of ventricular tachycardia precipitated by the administration of sodium iothalamate (Conray 420) in a patient already taking phenylamine, both of which drugs prolong the QT interval. Antiarrhythmic agents, beta blockers, tricyclic antidepressants and phenothiazines may all be associated with a prolonged QT interval. In patients treated with amiodarone, a class III antiarrhythmic agent, lengthening of the QT interval may be used clinically to estimate myocardial drug concentrations, serum levels reflecting drug activity poorly (Debbas *et al.*, 1984).

Tricyclic antidepressants prolong the QT interval. In normal subjects this increase is usually insignificant (Burkhardt *et al.*, 1978). However, in patients in whom the QT interval is already prolonged, administration may be calamitous, increasing the risk of ventricular arrhythmias (Motte *et al.*, 1970).

Ischaemic heart disease, cardiomyopathy, congenital heart block and electrolyte changes are all associated with QT prolongation. Altered myocardial repolarization also occurs in a wide variety of diseases affecting the central nervous system, particularly acute events such as subarachnoid haemorrhage or skull fracture (Harries, 1981).

Hypothermia, either occurring accidentally or induced experimentally, is characterized by delay of both the upstroke and downstroke of membrane action potential (Marshall, 1959). As a consequence there is prolongation of the QT interval.

The electrocardiographic changes, other than bradycardia, observed in patients with hypothyroidism include prolongation of the QT interval, but since the T wave amplitude is low, precise measurement of this interval is often impossible (Surawicz & Mangiardi, 1977).

Repolarization changes of hypokalaemia are accompanied on the surface electrocardiogram by ST segment depression, diminished T wave amplitude and increased prominence of the U wave with resultant prolongation of the QT (QU) interval. Hypocalcaemia is characterized by a long, flat ST segment resulting in QT prolongation. The other case report published in the current issue (O'Keefe *et al.*, 1984) concerning the LQTS emphasizes the vulnerability to cardiac arrhythmias associated with biochemical abnormalities.

'Giant T wave inversion'

The slow idioventricular escape rhythm in cases of complete atrioventricular block is at times associated with large, broad, bizarre and inverted T waves with marked prolongation of the QT interval. This phenomenon is usually best seen in leads V2 to V4 and is termed 'giant T wave inversion' (Jacobson & Schrire 1965, 1966). Giant T wave inversion also occurs particularly after a syncope in both clinical and experimental cerebral disorders (Birke & Stroma, 1955). A proposed genesis of these 'giant' inverted T waves and the associated prolonged QT_c is intense sympathetic stimulation resulting from the anoxia of a syncopal attack. Thus, the appearance of these T waves in cases of complete atrioventricular block may indicate that the patient has had a recent syncopal Stokes-Adams attack due to either ventricular standstill or ventricular fibrillation.

Others have described a type of 'cardiac memory' which may offer an alternative explanation for the T wave changes. The authors demonstrated massive T wave inversion and ST segment depression in association with cardiac pacing. The magnitude of T wave inversion was related to the amount of electrical power used for ventricular pacing and the time taken for complete regression after pacing was directly related to the duration of pacing (Chatterjee *et al.*, 1969; Rosenbaum *et al.*, 1982).

Ischaemic heart disease

Some survivors of ventricular fibrillation seem to have a sustained propensity for occurrence of ventricular fibrillation, probably reflecting a continued state of myocardial instability (Haynes *et al.*, 1978; Borggreffe *et al.*, 1984). In patients with coronary heart disease, ventricular ectopics are associated with an increased risk of sudden cardiac death (Vismara *et al.*, 1977; Chiang *et al.*, 1969; Oliver *et al.*, 1974). Yet a majority of middle aged adults with no apparent heart disease have dysrhythmias with little effect on mortality (Clarke *et al.*, 1976; Pribble *et al.*, 1975; Desai *et al.*,

1973). A predisposing state of vulnerability is therefore necessary for ventricular ectopics to initiate ventricular fibrillation. When compared with post myocardial infarction patients, the electrocardiograms of ventricular fibrillation survivors clearly show repolarization abnormalities including ventricular ectopy and QT_c prolongation (Haynes *et al.*, 1978; Schwartz & Wolf, 1978).

Prognosis and treatment of acquired LQTS

As distinct from congenital forms of LQTS, patients with acquired disease are usually seen in the fifth and sixth decades and childhood electrocardiograms, when available, do not show any QT prolongation. Because of the multitude of factors which may be responsible for QT prolongation in acquired disease, one must initially establish the cause of QT prolongation and direct attention to its specific management such as drug withdrawal, electrolyte balance or treatment of hypothermia.

Torsades de pointes in the acquired LQTS must not be treated with the standard drugs used for the control of ventricular tachycardia and fibrillation as they invariably exacerbate the disorder, presumably by increasing the temporal dispersion of repolarization (Soffer *et al.*, 1982). Instead, treatment which shortens repolarization is required, such as intravenous isoprenaline or rapid cardiac pacing.

In appropriate cases, for the termination of life threatening sustained ventricular tachycardia, both temporary pacing as well as permanently implanted devices for anti-tachyarrhythmia pacing, cardioversion or defibrillation may be used (Steinbeck *et al.*, 1983; Ludiomorsky *et al.*, 1982; Maloney *et al.*, 1980).

Conclusion

The pathophysiology of the congenital and acquired forms of the long QT syndrome is different, and this is reflected in the differences in their management. General anaesthesia presents special hazards, which may be avoided if the diagnosis is made pre-operatively.

Although relatively uncommon the LQTS carries a high risk for both morbidity and mortality. In spite of its importance and treatable clinical implications it is often overlooked, or diagnosed retrospectively, because measurement of the QT interval tends to be omitted from routine ECG reporting unless it is grossly abnormal. Abnormal QT prolongation is possibly the single most commonly missed marker of preventable dysrhythmic death.

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