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REVIEWS

Long QT: Good, Bad or Indifferent?

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A survey of current literature suggests an increasing interest in both the desirable and undesirable implications of a prolonged QT interval, the former perceived to be the beneficial effect of antiarrhythmic drugs that prolong the duration of ventricular action potential, and the latter considered to be a potential marker for sudden cardiac death in patients with ischemic heart disease. In addition, there has been an increasing interest in the congenital long QT syndrome associated with an apparent dysfunction of the autonomic nervous system and serious, potentially lethal ventricular arrhythmias. Circumstantial evidence suggests that these arrhythmias are due to increased dispersion of repolarization which may be aggravated by psychologic and emotional perturbations.

In this review, the associations between the long QT interval, autonomic nervous system, dispersion of repolarization, antiarrhythmic drugs and ventricular arrhythmias are examined. Attention is directed to the difficulties of accurate QT measurement, problems related to the correction of the QT interval for heart rate and sex (QT_c), the wide range of normal values and the modest QT alterations after various manipulations of the autonomic nervous system. Clinical conditions associated with marked, moderate and occasional QT lengthening are listed and discussed briefly in relation to the disturbances of nervous system, dispersion of ventricular repolarization and ventricular arrhythmias.

It is proposed that the absence of relevant animal models of neurogenic or psychogenic QT prolongation hinders the investigation of the neurogenic factors associated with QT lengthening. QT prolongation is most often induced by antiarrhythmic drugs and ischemic heart disease. However, it is not known whether the occurrence of torsade de pointes type of ventricular tachycardia in patients treated with antiarrhythmic drugs is related to a critical drug dose or a critical degree of QT_c prolongation. There is no conclusive evidence that QT lengthening has any predictive value either during the acute phase or during convalescence after myocardial infarction. Also, a serious deficiency in current knowledge is the lack of an established relation between the prolonged QT interval and the dispersion of ventricular repolarization. It is concluded that the number of unanswered questions discussed in this review still makes it difficult to judge when a prolonged QT interval is good, bad or indifferent.

The significance of a prolonged QT interval on the electrocardiogram may be variously interpreted in clinical practice. At times, QT lengthening is perceived as the beneficial result of the administration of an antiarrhythmic drug. Under other circumstances, a prolonged QT interval is considered an ominous sign because of its association with ventricular tachycardias exhibiting the specific configuration known as torsade de pointes. Most often, however, the corrected QT (QT_c) interval is an item on the electocardiographic report that is of uncertain significance and of little use in clinical decision-making.

"Historically, interest in the QT has waxed and waned," stated Burchell (1) in a recent review article on the subject. A survey of current literature suggests that the interest cycle is on the upswing, with attention focused on both the "good" and the "bad" implications of a prolonged QT interval. In one of two recent editorials on this subject, Vaughan Williams (2) discussed the prolonged QT interval as a manifestation of prolonged repolarization reflective of a potentially beneficial effect of antiarrhythmic drugs that prolong the duration of ventricular action potential. In the other, Schwartz (3) considered lengthening of the QT interval as a potential marker for identifying survivors of myocardial infarction at high risk for subsequent cardiac events.

It would seem timely and of clinical and research relevance to critically examine the strength of the presumed associations between the "good" and the "bad" implica-

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tions of a prolonged QT interval, the factors that may in part contribute to the uncertainties relative to the implications of a prolonged QT interval, and identify areas where knowledge of the mechanisms for and clinical significance of the prolonged QT interval is lacking.

Measurement of QT and Its Correction for Heart Rate (QT_c)

As background information for a discussion of the significance of and problems related to QT prolongation, it may be helpful to understand the essential nature of the QT interval and the conditions for its proper measurement since certainly some of the disparities in interpretation of QT significance derive from inconsistencies in its measurement. The numerous potential sources of inaccuracy of QT measurement in the clinical setting make it difficult to evaluate the biologic significance of minor QT changes, even when they are "statistically significant."

Accurate measurement of the QT interval requires a multichannel recorder. Determination of the onset of the QRS complex and the end of the T wave is difficult to accomplish unless several limb and precordial leads are recorded simultaneously (4,5), preferably at a paper speed of 50 mm/s or greater. In addition, because the adjustment of QT duration to changes in RR interval is not instantaneous but gradual QT_c measurements represent steady state values only when the rhythm remains regular for several cardiac cycles.

The QT interval includes the QRS duration, and although a prolonged QRS complex does not detract from the accuracy of QT measurement, it may change the interpretation of the measured value. Subtraction of QRS duration from the QT interval may be required in estimating the duration of repolarization, independent of the duration of depolarization. However, this procedure also introduces potential inaccuracy because of the difficulties inherent in the determination of the end of the QRS complex (6).

Role of heart rate. The QT interval decreases with increasing heart rate. Of the many formulas proposed to describe this relation in normal human subjects and, therefore, to correct for heart rate (that is, square root, cube root and other exponential, logarithmic or linear formulas [references in reference 7]), none has achieved a perfect fit within a wide range of RR intervals. As pointed out by Lepeschkin (7), these formulas cannot be exact because they give infinite QT values at RR = ∞, and values exceeding RR at RR values below 0.17 to 0.23 second. The limitations of methods designed to correct the interval QT for heart rate probably reflect the complex relation between heart rate and the duration of ventricular action potential, the basis for the rate dependency of the QT interval. The relation best fits a hyperbola that reaches a hypothetical maximal value after a very long cycle length (8), and that appears to approach a certain minimal value at very short cycle lengths although this is difficult to investigate as depolarization encroaches on previous repolarization at extremely short RR intervals.

Normal QT_c range. Lepeschkin (7) compiled 5,000 reported cases and added 1,100 personal cases to define the normal range of QT distribution within a wide range of RR intervals. Although the various formulas proposed for describing the dependence of the interval QT on the RR interval lie within the range of normal limits compiled by Lepeschkin at most RR intervals, both the square root formula and the linear formula appear to be more suitable over a wider range of RR intervals than do the logarithmic and cube root formulas. Another interesting feature of Lepeschkin's study is the wide range for normal QT_c values. Although it is conceivable that some of the cases included by Lepeschkin represented values from individuals with an abnormal QT interval, the study showed that the normal range of QT_c was within ±15% of the mean value over a wide range of RR intervals. This represents approximately 50 ms at an RR interval of 400 ms and 140 ms at an RR of 1,200 ms. This wide range of "normal" makes it difficult to interpret the significance of differences between groups of patients or individuals when all values remain within normal ranges.

Bazett formula. The most widely used formula for the correction for rate is that of Bazett in which:

$$QT_c = k\sqrt{RR}.$$

The k value of the Bazett formula, as modified by Shipley and Hallaran (9), is 0.397 for men and 0.415 for women. Many investigators consider the upper limit or normal value of QT_c for both sexes as 0.44 second. However, this value is below the upper limit of the normal QT value in the study of Lepeschkin (7), and the latter would give normal QT_c values of approximately 0.46 for men and 0.47 for women. The Bazett formula can be used to study the effects of interventions modifying the duration of the QT interval through effects on the k value. This type of evaluation may be more informative when studying the effects of drugs and interventions than the QT_c measurements alone made at only one RR interval. The appropriate k value can be found by regression analysis of the measured intervals using the function defined by Bazett's formula with a k value of 0.40 serving as reference (10). Using this method, Ahnve (10) found a k value of 0.406 for postmyocardial infarction patients treated with metoprolol, 0.434 for patients on the second day after myocardial infarction and 0.454 for patients with acute myocardial infarction treated with quinidine (Fig. 1).

QT Interval as a Reflector of Repolarization

The QT interval as recorded on the surface electrocardiogram represents the sum of uncanceled potential differ-

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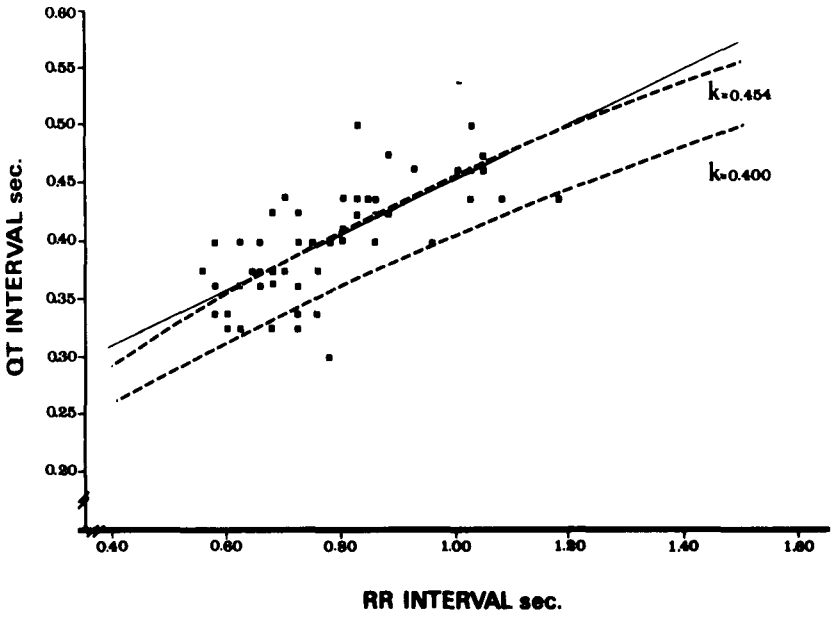

Figure 1. The relation between QT and RR intervals in 53 patients with acute myocardial infarction treated with quinidine, but without bundle branch block or digitalis therapy. The regression line (QT = 0.25 · RR + 0.2075) and the function defined by Bazett's formula with a k value of 0.400 serve as references. The estimated k value here is 0.454. (Reprinted with permission of Ahnve S, et al. [29].)

ences during ventricular depolarization and repolarization. In utilizing the QT interval as a reflector of repolarization, it is important to know whether the end of the T wave corresponds to the longest duration of ventricular repolarization (7) or whether it is followed by a period of "silent repolarization" resulting from canceled potential differences (11). The existence of silent repolarization would make it difficult to utilize the QT interval in any meaningful way as a reflector of altered repolarization. Although a systematic exploration of the entire ventricular myocardium has not been performed to resolve the question of silent repolarization, in our opinion there is no direct experimental evidence that ventricular repolarization continues after the end of the repolarization wave inscribed on the surface electrocardiogram in animals or human subjects.

Is there "silent repolarization"? The existence of "silent repolarization" has been postulated to explain apparent QT lengthening in dogs after left stellate ganglion stimulation, a procedure that shortened the effective refractory period in the area supplied by the stimulated nerves (11) and, therefore, "unmasked" previously canceled repolarization. This finding, however, has not been confirmed in human subjects (12). The concept of silent repolarization would be difficult to reconcile with a considerable amount of data supporting the concept that the end of the T wave is the end of repolarization. In studies performed in our laboratories, all recorded endocardial monophasic action potentials from the left and right ventricle in human subjects (13), monophasic action potentials from the ventricular surface in dogs (14) and transmembrane action potentials from the ventricular surface in rabbits (15) terminated before the end of the T wave. Also, in a recent study of Savigny et al. (16), QT intervals recorded at different temperatures and potassium concentrations in guinea pig hearts paralleled the duration of the ventricular action potential in excised right ventricular papillary muscles, but under all examined conditions, action potential duration was markedly shorter than the QT interval.

To prove or disprove the presence of silent repolarization would require the impossible task of exploring the duration of repolarization from all fragments of ventricular myocardium. However, in the absence of contradicting evidence, it appears reasonable to assume that the end of the T wave closely approximates the longest duration of ventricular repolarization. This is a useful concept for interpreting the significance of a prolonged QT interval.

Relations Between QT and Duration of Systole

It has been proposed in the postmyocardial infarction patient that a QT interval exceeding the QS_2 interval is a predictor of unfavorable prognosis (17). While requiring further confirmation, if the observation is shown to be valid, the factors influencing the relations between QT duration and duration of systole need to be assessed to understand the rationale for linking these two variables.

Relation between duration of QT and duration of ventricular ejection. A close correlation has been established (5,17) between the duration of the QT interval and the duration of ventricular ejection at different heart rates under *normal* conditions. Similar relations are maintained under the influence of positive inotropic interventions (for example, catecholamines, calcium and digitalis [18]), all of which result in a parallel shortening of QT and mechanical systole. An opposite but parallel effect, that is, lengthening

of both the QT interval and mechanical systole, occurs during hypocalcemia (19). Under most other pharmacologic or pathologic conditions, however, there is no close correlation between the durations of QT interval and ventricular ejection. The duration of ejection is influenced by a number of hemodynamic factors that are independent of repolarization, and vice versa. The factors that are frequently responsible for the prolongation of the QT interval, such as prolonged duration of phase 3 of repolarization or an altered sequence of repolarization, have only limited influence on the duration of ejection. Thus, in conditions associated with a prolonged QT_c other than hypocalcemia, the QT interval usually exceeds the duration of the QS_2 interval.

We conclude that a prolonged QT interval in patients with impaired mechanical function is an independent reflector of repolarization and is not necessarily influenced by altered contractility.

Autonomic Nervous System Influences on QT

As the significance of a prolonged QT interval is related in many instances to the underlying autonomic nervous system "balance," knowledge about autonomic nervous system influences on the QT interval also needs to be summarized before examining the clinical syndromes associated with a prolonged interval.

Vagal effects and changes in heart rate. Ventricular repolarization is believed to be predominantly under beta-adrenergic control (20). Under normal conditions, vagal effects are predominantly indirect and secondary to changes in heart rate (21). The effects of atropine on the QT interval have been attributed exclusively to the increase in heart rate (22). However, even though the administration of atropine does not change QT_c using Bazett's formula, the drug does shorten the QT interval during pacing at constant rates (23,24). These observations demonstrate that the effects of interventions on the QT interval during controlled heart rate may differ from the effects during spontaneous heart rate changes (23,24).

Beta-receptor blocking drugs. Despite some minor discrepancies among studies, all investigators are in agreement that the beta-adrenergic blocking drugs produce no major changes in QT_c. In two studies made at a constant heart rate maintained by pacing, intravenous administration of propranolol caused either no significant change in QT_c (23) or a slight QT_c prolongation (25). In nonpaced subjects, propranolol shortened QT_c from 0.40 to 0.37 in one study (26) and from 0.418 to 0.394 in another study (27). No QT_c differences were found between subjects being treated with beta-adrenergic drugs and untreated subjects (28). Two other studies (29,30) examined the survivors of myocardial infarction. In one (29), QT_c was slightly shorter (0.394) in the patients treated with metoprolol than in the group receiving placebo (0.406). In the other (30), alprenolol treatment shortened QT_c from 0.415 to 0.39 in a subgroup of the most severely diseased patients but had no effect on QT_c in the remaining patients.

Transplanted hearts. Similar to the minor and inconsistent effect of beta-adrenergic blocking drugs on the QT interval, other types of autonomic deprivation also have minimal effects on QT_c. In transplanted hearts paced at a cycle length of 500 ms, QT and QT_c intervals have been shown to be normal, averaging 334 ± 18 ms and 0.43 ± 0.03, respectively (31). Also, the duration of the QT interval appears to be normal in published tracings of nonpaced donor hearts (32).

Stellate ganglion block. In a study in normal subjects (33), no change in QT_c was produced by left stellate ganglion block, while right stellate ganglion block prolonged the average QT_c from 0.40 to 0.43 in 15 subjects.

Prolonged QT Interval in Clinical Practice

With the preceding background information in hand, clinical states associated with QT interval prolongation will now be discussed relative to the strength of the association between presumed mechanisms and the clinical manifestation of a prolonged QT interval. For ease of description, the conditions will be divided into those that result in: 1) marked QT_c prolongation (that is, > 125% of the average normal value), and 2) moderate QT_c prolongation (that is, approximately 115 to 125% of the average normal value). In addition, several reported causes for minor and inconsistent QT_c prolongation are considered separately. Subdivision into these categories is based exclusively on personal experience and is not categorical. No data are available to estimate the sensitivity or specificity of either marked or moderate QT_c prolongation associated with the conditions listed in Tables 1 and 2. Each of the conditions that can cause marked QT prolongation may also cause a lesser degree of QT prolongation or no QT prolongation. However, the conditions listed or causing moderate QT prolongation in Table 2 seldom cause as marked QT prolongation as do the conditions in Table 1. Thus, the list of conditions in Tables 1 and 2 may be used as a guideline in the differential diagnosis when

Table 1. Causes of Marked QT_c Lengthening* (>125%)

1. Congenital
2. Neurogenic, including organophosphorus
3. Severe hypothermia
4. Severe hypocalcemia
5. Fad diets
6. Contrast injections into coronary artery
7. Antiarrhythmic drugs (seldom)
8. Severe bradycardia, atrioventricular block, myocardial ischemia, postresuscitation, unexplained† (occasionally)

*Excluding that secondary to QRS widening. †Probably predominantly neurogenic.

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Table 2. Causes of Moderate QT_c Prolongation* (≤125%)

1. Post-ischemic—transmural and nontransmural myocardial infarction
2. Various cardiomyopathies and after cardiac surgery trauma
3. Moderate hypocalcemia
4. Class I antiarrhythmic agents, tranquilizers
5. Hypothyroidism and pituitary insufficiency (occasionally)
6. Neurogenic or unexplained (occasionally)

*Excluding that secondary to QRS widening.

confronted with marked or moderate QT_c prolongation of uncertain origin.

Congenital Long QT Syndrome

The congenital long QT syndrome represents a unique clinical condition in which the available evidence strongly suggests that the lengthening of the QT interval is neurogenic, that the long QT interval is associated with increased dispersion of repolarization and that this increased dispersion is the principal, if not the only, cause of the associated life-threatening ventricular arrhythmias (Table 3).

The first report of the familial prolongation of QT interval associated with congenital deafness and sudden cardiac death due to ventricular arrhythmia was published by Jervell and Lange-Nielsen of Norway (34). The disorder, however, had apparently been recognized in the United States (35) before this first publication. Subsequently, families with the same disorder but with normal hearing were reported in Ireland (36) and Italy (37), and these two reports generated the eponym of Romano-Ward syndrome. Both the Jervell-Nielsen and Romano-Ward syndromes have been reviewed extensively (38,39) and an informal registry of all reported cases has been established by Schwartz (3). We will limit our discussion to incompletely resolved problems relevant to the understanding of the mechanism of the syndrome.

Clinical features. The natural history of the disorder is extremely variable and the appearance of symptoms is sporadic and unpredictable. The marked spontaneous variations in the duration of QT interval (Fig. 2) make it difficult to establish a direct cause and effect relation between a critical

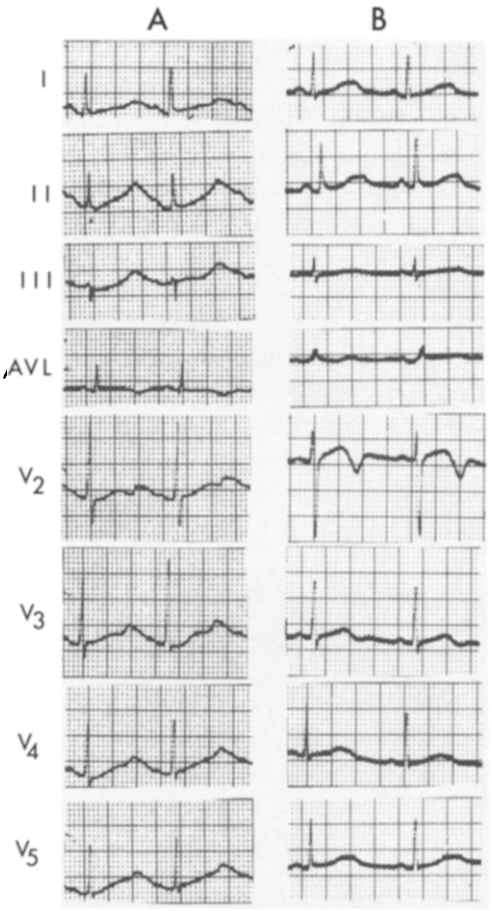

Figure 2. Electrocardiograms from a 15 year old girl with a congenital long QT syndrome on two different days but no change in treatment. Note greater QT lengthening in **A** than in **B**.

lengthening of the QT interval and the appearance of serious arrhythmias. Nevertheless, it would be difficult to invoke coincidence as an explanation for the numerous clinical observations of ventricular arrhythmia, syncope and sudden death provoked by increased sympathetic stimulation (40) and emotional stress, such as fright (34,35,38,41) or startling noises (41,42). In some cases, continuous recordings are available (42–44) to show precipitation of a prolongation of the QT interval by noxious psychic stimuli and a con-

Table 3. Relation Between Prolonged QT Interval, Autonomic Nervous System, Dispersion of Repolarization and Ventricular Arrhythmias

Marked QT_c Prolongation	Predominantly Neurogenic	Increased Dispersion of Vent. Repolarization	Serious Vent. Arrhythmias
Congenital LQTS	Yes	Yes	Yes
CVA pattern (transient, acquired)	Yes	?	No evidence
Drugs and metabolic factors*	No	Probably yes	Yes
AV block and severe bradycardia	No	Probably yes	Yes
Myocardial disease (usually less marked QT_c lengthening)	No	Probably yes	Yes, but no established relation to QT_c

*Excluding organophosphorus poisoning. AV = atrioventricular; CVA = cerebrovascular; LQTS = long QT syndrome; Vent. = ventricular.

comitant appearance of ventricular premature complexes and ventricular tachycardia degenerating into ventricular fibrillation.

Evidence for autonomic dysfunction in patients with long QT syndrome include: the reported inability to increase heart rate appropriately with exercise (39) or after administration of atropine (45) and inappropriate adjustment of the QT interval to tachycardia induced by exercise or during the Valsalva maneuver (46). Such dysfunction does not occur uniformly in all patients, however, probably reflecting variable expressions of altered autonomic control.

Anatomic findings. Except for the changes in ventricular repolarization, the electrocardiogram of patients with long QT syndrome is usually normal and there is no clinical evidence of valvular, myocardial or coronary heart disease. In several autopsy studies (38,39), the myocardium appeared normal both grossly and histologically. However, in one series (38), a consistent finding was focal neuritis and neural degeneration within the sinoatrial node, atrioventricular node, His bundle and ventricular myocardium. Others reported degeneration of Purkinje fibers (47,48) or fibrosis of the conduction system (49).

Mechanism of Arrhythmia in Long QT Syndrome

Increased dispersion of repolarization. Electrocardiograms recorded at the onset of the characteristic polymorphous ventricular tachycardia (torsade de pointes) or ventricular fibrillation show that these arrhythmias usually are precipitated by a ventricular premature complex interrupting the T wave (40,45,50–54). If it is assumed that the onset of premature ventricular depolarization corresponds to the recovery of excitability in some portion of the ventricle, while the end of the QT interval corresponds to a similar instant in some other portion of the ventricle, the interval between the onset of the ventricular premature complex and the end of the QT interval can also be assumed to represent the minimal duration of dispersion of repolarization. The method of estimating this interval is shown in Figure 3. Personal observations and examination of published figures of the ventricular premature complex in patients with the congenital long QT syndrome suggest that this minimal dispersion of repolarization is large. For example, the approximate values of minimal dispersion in published illustrations showing the onset of torsade de pointes in patients with the congenital long QT syndrome (Fig. 3 in reference 50, Fig. 5 and 12 in reference 40, Fig. 4 in reference 51, Fig. 3 in reference 52, Fig. 4 in reference 53 and Fig. 2 in reference 45) ranged from 80 to 360 ms (average 230). Although these values lack precision when measured from published records, they do provide some insight into the qualitative aspects of the underlying problem. It is interesting that the values resemble the reported differences between the durations of the QT interval and the effective refractory period in the right or the left ventricle (52). Other evidence in support of marked asynchrony of repolarization in these patients includes differences in the durations of monophasic action potential in different portions of the ventricles (55,56) and marked variability of the effective refractory period found during the exploration of the right ventricle (57,58).

Conditions required for dispersion of repolarization. In support of dispersion of repolarization as a mechanism for arrhythmogenesis in the long QT syndrome, recent studies (59) utilizing an animal model of dispersion due predominantly to unequal duration of ventricular monophasic action potentials have shown that the induction of sustained ventricular arrhythmia required: 1) dispersion that was about three to four times greater than control dispersion and, 2) a single premature ventricular stimulus at the site of the short monophasic action potential durations. To prove that the same conditions are required to initiate ventricular arrhythmias in subjects with the long QT syndrome, it will

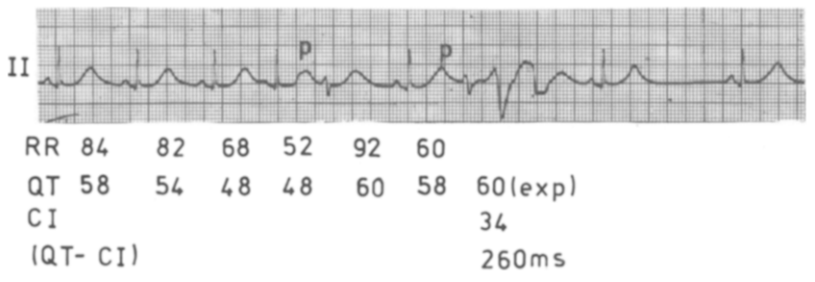

Figure 3. Electrocardiographic strip of lead II from a 68 year old woman with prolonged QT interval of uncertain origin after resuscitation from cardiac arrest initiated by ventricular tachycardia (torsade de pointes). The duration of six consecutive RR and QT intervals (in cs) is shown at the **bottom** of the strip. The two complexes preceded by a premature P wave (P) represent atrial extrasystoles conducted with ventricular aberration. The T wave of the second postextrasystolic complex is interrupted by a ventricular premature complex (R on T phenomenon), which is followed by another ventricular premature complex. Assuming that the QT interval of the second postextrasystolic complex equals the QT interval of the first postextrasystolic complex (RR = 92, QT = 60), the expected (exp) QT = 60. Because the coupling of the ventricular premature complex (CI) = 34 cs, the minimal dispersion (QT − CI) = 60 − 34 cs, that is, 260 ms.

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be necessary to determine the magnitude and distribution of dispersion of repolarization as well as the mechanism of the ventricular premature complex initiating the arrhythmia. Conceivably, in patients with the long QT syndrome, increased sympathetic stimulation at the onset of arrhythmia could increase diastolic depolarization and precipitate an automatic discharge of a latent pacemaker fiber. Alternatively, the increased dispersion might precipitate reexcitation or reentry. It has been suggested (43,52,60) that the reentry in this condition may be caused by asynchronous recovery of the His-Purkinje-bundle branch system rather than of ventricular myocardium.

The problem in understanding the mechanism of arrhythmogenesis in the long QT syndrome and, indeed, in other syndromes potentially secondary to autonomic influence, is that no known autonomic interventions have produced comparable degrees of QT_c prolongation or abnormalities of ventricular repolarization coupled with the appearance of spontaneous ventricular arrhythmias. The only acquired condition that appears similar to the syndrome is poisoning with organophosphorus compounds that cause QT prolongation and "torsade de pointes" (61). This disorder is probably neurogenic because the organophosphorus compounds inhibit cholinesterase and produce intense vagal stimulation. The similarity of the electrocardiographic pattern in this condition with that of the long QT syndrome suggests that the abnormality of the long QT syndrome may be due to some peculiar combination of abnormal vagal and adrenergic imbalances.

Role of therapeutic interventions. Because of the spontaneous variation in QT duration and ventricular arrhythmias, the evaluation of therapeutic interventions is also difficult in the long QT syndrome. The ventricular arrhythmia is seldom inducible in the laboratory and, thus, defies assessment based on pharmacologic prevention of inducibility. The administration of beta-adrenergic blocking drugs appears to represent a rational form of therapy because the attacks of life-threatening arrhythmias are frequently precipitated by increased sympathetic stimulation. Also, it can be reasoned that such treatment will be helpful if the critical dispersion of repolarization is caused by the presence of a mixture of two types of cardiac fibers, those that cannot shorten in response to beta-adrenergic stimulation and those that respond normally. In such a case, beta-adrenergic blockade may prevent the shortening of normally responding fibers and thereby prevent an increase in dispersion of repolarization accompanying sympathetic stimulation. The effectiveness of beta-adrenergic blocking drugs has been substantiated by many investigators (39,40,53,62,63), even though beta-adrenergic blockers do not necessarily shorten the QT interval in these patients (45,53). Also, sedatives appear to be helpful, probably because they blunt the emotional responses (43,62,64,65).

The excision of the left or right stellate ganglion has been helpful in a few cases (62), but the effects of such therapy are not predictable and there are numerous reports (12,21,39,62,64–67) attesting to the failure of either changing the QT interval or preventing arrhythmias after such interventions, or both.

Acquired Neurogenic QT Lengthening

Cerebrovascular accident. In 1954 Burch et al. (68) identified a specific electrocardiographic pattern peculiar to certain patients with a cerebrovascular accident. This pattern occurs most frequently in patients with intracranial hemorrhage (references in reference 69), but it has also been found in patients with other intracranial lesions. The typical electrocardiographic pattern is characterized by a conspicuous increase in T wave amplitude, prolongation of the QT interval by 20% or more (Fig. 4) and an occasional increase in U wave amplitude. However, it appears in only a small minority of patients with central nervous system disease. We found this pattern in 29 (32%) of 89 patients with intracranial hemorrhage, 10% of patients with primary intracranial aneurysm and 7% of patients with acute cerebral thrombosis and increased intracranial pressure (69). The pattern was found in only 1 of 30 patients with hypertensive encephalopathy and in 1 of 32 patients with brain metastases (69). Similar percentages have been found by other investigators. In one study of 186 patients with cerebrovascular hemorrhage (70), the QT interval was prolonged only in patients with frontal lobe damage. In another study of 89 patients with subarachnoid hemorrhage (71), QT_c exceeded 115% of normal in 19.1% of patients, and in an additional study (72), QT_c was prolonged in 11 of 20 patients.

The finding that the cerebrovascular accident pattern appeared in several patients after cryohypophysectomy associated with diabetes insipidus (73) suggested that it could be due to injury of the hypothalamus. This would explain the association of the pattern with subarachnoid hemorrhage because hypothalamic lesions occur frequently after rupture of aneurysms of the anterior and posterior communicating arteries (74). On rare occasions, however, an electrocardiographic pattern identical to that occurring in patients with cerebral lesions may appear after extracranial manipulations of the autonomic nervous system, for example, after transabdominal truncal vagotomy for treatment of peptic ulcer disease (75) or after presumed destruction of the sympathetic nerve fibers during radical lymph node dissection of the right side of the neck (76). The typical cerebrovascular accident pattern is usually a transient phenomenon lasting only a few days, and can be reversed by means of intravenous administration of small doses of isoproterenol (77).

Incidence of ventricular arrhythmias in cerebrovascular accident. Unlike the congenital long QT syndrome, a review of the literature and personal observations suggest that the QT prolongation in patients with the central nervous system pattern is seldom associated with serious ventricular

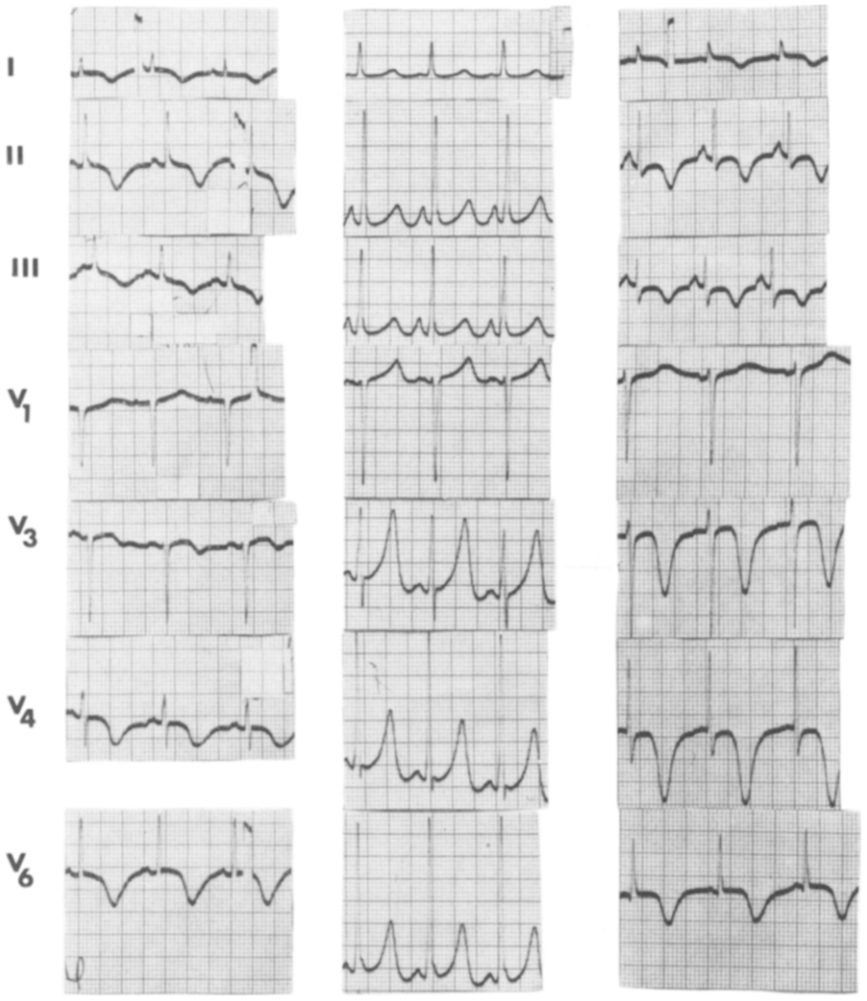

Figure 4. Typical electrocardiographic pattern of cerebrovascular accident in three women aged 45, 39 and 44, respectively, with subarachnoid hemorrhage. Note the prolonged QT and increased T wave amplitude.

arrhythmias. Although the pattern usually occurs in seriously ill individuals requiring hospitalization, we found only four case reports (78–81) of associated serious ventricular arrhythmias. In one of these studies (79), another patient with subarachnoid hemorrhage admitted to the coronary care unit had ventricular fibrillation but the electrocardiographic description does not mention the duration of the QT interval. In another report (82) of two patients with subarachnoid hemorrhage and serious ventricular arrhythmias, one patient had a normal electrocardiogram within 1 hour after ventricular tachycardia was observed on a monitor, and in the other patient with syncope attributed to ventricular flutter, the QT interval was not prolonged on the illustrated electrocardiogram.

Most studies of patients with stroke, including those with intracranial hemorrhage, contain no information about the presence or absence of arrhythmia. However, in a few studies the results of electrocardiographic monitoring are available. In one such study (83) of 135 patients with stroke of whom 14 had subarachnoid hemorrhage, ventricular tachycardia occurred in 3 but their electrocardiographic pattern is not described. In that study (83), 69% of patients had heart disease and monitoring did not "improve the 30 day mortality." In one of two other studies, only transient single ventricular ectopic complexes were reported in 2 of 20 patients with subarachnoid hemorrhage (72), and in the other, neither ventricular tachycardian or fibrillation is listed among the findings in 52 stroke patients, of whom 9 had cerebral hemorrhage (84). Kuo et al. (85), monitored 28 patients with long QT_c (0.53 ± 0.06), predominantly due to central nervous system disorders, and found no increased incidence or arrhythmia in this group.

Mechanism of the cerebrovascular accident electrocardiographic pattern. As with the long QT syndrome, the inadequacy of experimental models for the repolarization alteration associated with cerebrovascular accidents hinders mechanistic studies. Several studies since the beginning of this century have shown that abnormally tall or deeply inverted T waves can be produced by means of various manipulations of autonomic innervation to the heart in dogs (11,86–88) and cats (39). Such T wave abnormalities are similar to the tall upright or deeply inverted T waves in the

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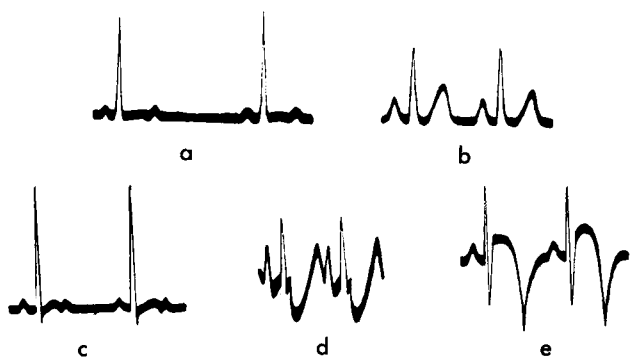
typical cardiovascular pattern. However, the marked QT_c prolongation typical of the pattern in human subjects does not accompany the neurogenic T wave abnormalities in these anesthetized animals.

It is possible that the difference between the experimental and the clinical electrocardiographic pattern associated with central nervous system disease may be due to differences in heart rate or measurement accuracy. Heart rate is frequently either normal or slow in patients with the cerebrovascular accident pattern, but it is usually rapid in animals with T wave abnormalities induced by stimulation or transection of the autonomic nerves supplying the heart. At rapid heart rates, T waves tend to encroach on P waves, and the precise measurement of QT interval becomes difficult. This problem is illustrated in several figures in the studies of Rothberger and Winterberg (86) (Fig. 5) and also of Yanowitz et al. (11). In a study by Ueda et al. (87), although heart rate was not controlled and QT measurements were not reported, their Figure 5 shows no change in heart rate and no increase in the QT interval after stellate ganglion stimulation. Yanowitz et al. (11), controlling heart rate by means of atrial pacing, were able to measure the QT interval in 15 of 46 dogs in which they performed left stellate ganglion stimulation. In these animals, the QT interval increased by 10 to 90 ms (average 46). Such wide disparity of QT values may be due to measurement problems because the QT interval was measured only in one (longitudinal) lead in which the T wave tends to be of low amplitude, sometimes isoelectric, frequently diphasic or notched. This morphology can cause an apparent shortening of the QT interval (14). The subsequent increase in T wave amplitude after neurogenic manipulation may more distinctly reveal the end of the T wave and, thus, simulate an apparent QT prolongation. Therefore, the finding of QT prolongation in dogs after left stellate ganglion stimulation needs to be confirmed in studies utilizing several synchrouous leads. The outcome of such study may not prove to be clinically relevant because left stellate ganglion stimulation has not prolonged the interval in human subjects (12).

Figure 5. Electrocardiographic changes in a dog with high vagal tone (**a**), high sympathetic tone (**b**), inhibition of sympathetic tone after isolation of both stellate ganglia (**c**), stimulation of right stellate ganglion (**d**) and stimulation of left stellate ganglion (**e**). See text. (Modified from Rothberger J, Winterberg H [86] with permission.)



In a study by Kuo and Surawicz (88), the pattern most similar to that of cerebrovascular accident in patients appeared in the experimental animal with combined left stellate ganglion transection and right stellate stimulation (Fig. 6). This procedure induced a conspicuous change in T wave amplitude and shortened the PR interval, but it prolonged the QT interval by only about 6%. Nevertheless, the similarity of the T wave configuration suggests that the pattern of cerebrovascular accident in human subjects may also be due to some combination of stimulation and inhibition of different portions of sympathetic centers, presumably in the hypothalamus.

A pattern more closely resembling the typical cerebrovascular pattern in patients was produced in dogs by administration of calcium after pretreatment with isoproterenol (89), the result being giant T waves with a prolonged QT interval. This paradoxical effect of two agents known to shorten the duration of ventricular action potential and QT_c when used separately is not easily understood.

Prolonged QT and Antiarrhythmic Drugs

Although a review of the literature suggests that the torsade de pointes type of tachycardia occurs characteristically during treatment with those antiarrhythmic drugs that prolong the QT interval, a relation between the arrhythmia and some critical QT_c value or some critical increment in QT_c has not been established. Of the commonly used drugs approved for treatment of ventricular arrhythmias, torsade de pointes has been illustrated or reported during administration of quinidine (90–96), procainamide (93,95–97) and disopyramide (94–98). Each of the these drugs not only prolongs the QT interval, but also slows intraventricular conduction as manifested by increased QRS duration. However, torsade de pointes also can occur during treatment with drugs that prolong the QT interval but have either slight effect on the QRS duration, (for example, amiodarone [99,100]) or no effect on the QRS duration (for example, sotalol [101]). No correlation between the occurrence of torsade de pointes and either the dose or the blood drug concentration has been established for any of the antiarrhythmic drugs. Sometimes the quinidine- or disopyramide-induced arrhythmia is attributed to large doses of the drugs (94), but frequently the adverse response is considered to be idiosyncratic (90,92,94). It has been suggested that some individuals are particularly susceptible to drug-induced QT prolongation (98) or that the drugs may unmask a latent form of congenital long QT syndrome (95). However, the paucity of information about drug-induced torsade de pointes led Smith and Gallagher (95) to speculate that, "it is not inconceivable that the mech-

anism responsible for the characteristic morphology. . . .may ultimately be proved to be independent of QT prolongation."

Psychotropic Drugs

The electrophysiologic effects of phenothiazines and tricyclic antidepressants are similar to those of quinidine-like antiarrhythmic drugs (references in reference 102). Several phenothiazine derivatives produce dose-dependent abnormalities of ventricular repolarization associated with QT_c prolongation. The abnormalities occur most commonly after administration of thioridazine and are less pronounced in patients treated with chlorpromazine and trifluoperazine. The role of phenothiazines in sudden cardiac death due to ventricular arrhythmia is not clear because of the small number of reported cases relative to the large number of treated individuals.

In one study (103) of 14 patients treated with either thioridazine doses averaging 710 mg/day or chlorpromazine doses averaging 960 mg/day, QT_c was 0.43 ± 0.4 and decreased to 0.41 ± 0.2 when the drugs were discontinued. This difference did not reach the level of statistical significance. It appears that the marked QT_c lengthening reported in some individuals with ventricular arrhythmias is frequently due to a concomitant administration of other drugs or electrolyte imbalance, or both (104). However, an unusual individual susceptibility, that is, an idosyncratic reaction, may also be responsible for some of the adverse drug effects.

Prolongation of QT_c by toxic doses of tricyclic antidepressant drugs is due mainly to widening of the QRS complex. Serious ventricular arrhythmias in patients treated with these drugs appear to be uncommon, and have been associated with drug overdose in most published reports.

Metabolic Disturbances

Marked QT_c prolongation can be due to hypocalcemia (105), severe hypothyroidism (106) and certain metabolic disturbances not associated with electrolyte imbalance, for example, "liquid protein" diet for weight reduction (107–109). The occurrence of ventricular tachycardia and torsade de pointes has been reported in all of these conditions (106–110). Injections of high sodium-containing or calcium-binding contrast agents into the coronary arteries (13,111) can also cause a transient marked QT_c prolongation attributed to lengthening of action potentials in the contrast-perfused regions of the ventricles (13). No arrhythmias were observed in the study (111) with prolongation of QT_c of up to 30%. However, in one recent case report (112), QT prolongation after intracoronary contrast injection was associated with a lowered electrical threshold for ventricular fibrillation.

Prolonged QT_c and Myocardial Damage

In many patients with rheumatic, congenital and hypertensive heart disease and various cardiomyopathies, QT_c is

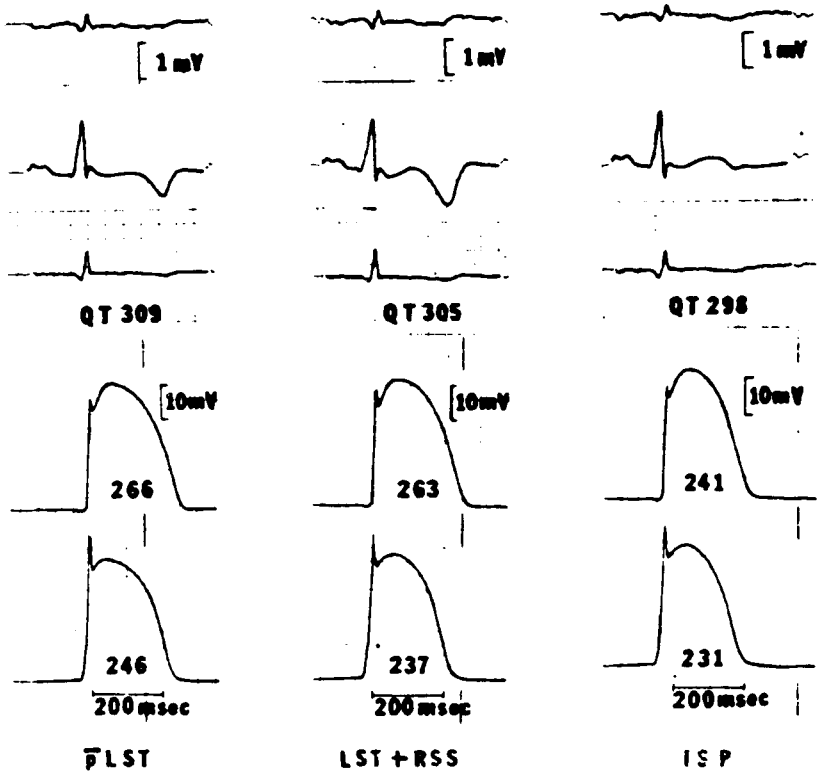


Figure 6. From **top to bottom,** leads X, Y and Z and monophasic action potential on the posterior and anterior walls of the left ventricle in a dog. Effects of left stellate ganglion transection (LST) alone (**left panel**), subsequent right stellate ganglion stimulation (RSS) (**middle panel**) and administration of isoproterenol (ISP) (μg) after right stellate ganglion stimulation (**right panel**). Tracings are retouched for clarity. All values are in ms. (Reprinted from Kuo CS, Surawicz B [88] with permission.)

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slightly to moderately prolonged. This is frequently due, at least in part, to prolongation of the QRS complex. However, asynchronous repolarization unrelated to the abnormal sequence of activation may also be important. Evidence for prolongation of the ventricular action potential from a muscle band excised in a patient with obstructive hypertrophic cardiomyopathy has been obtained (113). Conversely, although ventricular hypertrophy and cardiomyopathy are frequently associated with an increased prevalence of ventricular arrhythmias, no correlation between these arrhythmias and prolongation of the QT interval has been reported. Moderate or, occasionally, marked QT_c lengthening occurs transiently in many patients after open heart operations, but we are not aware of studies correlating the degree of QT_c prolongation with postoperative arrhythmias, morbidity or mortality.

QT Interval and Ischemic Heart Disease

Acute myocardial ischemia is usually associated with ST segment deviation and shortening of the QT interval, but subacute or chronic myocardial infarction is characterized by T wave abnormalities and QT_c prolongation (Fig. 7). In experimental infarction in dogs, QT_c prolongation is accompanied by prolongation of the effective refractory period (114) and of ventricular action potential at the margin of the infarction (115). The QT_c prolongation resulting from transmural or nontransmural myocardial infarction may persist for days, months or years. To the best of our knowledge, there are no prospective studies on the natural history of QT_c in survivors of myocardial infarction.

Role of QT prolongation in prognosis. There are at least two reasons for proposing that QT_c lengthening may be predictive of adverse prognosis in the survivors of myocardial infarction. One could assume that a longer QT_c interval is associated with a more extensive mass of scarred or poorly functioning myocardium. However, it is not known whether the magnitude of QT_c lengthening bears a relation to the age, location and extent of the infarction. In addition, if the QT lengthening is secondary to a more extensive mass of affected myocardium, the prolonged QT_c would not be expected to represent an independent prognostic marker. Alternatively, one could assume that the lengthening of QT_c reflects an increased dispersion of ventricular repolarization, a marker of a potentially arrhythmogenic electrophysiologic state as just discussed.

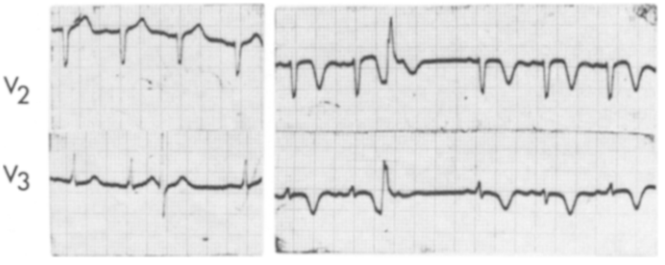
A study (116) of 32 patients with acute myocardial infarction suggested that the initial QT_c prolongation was predictive of ventricular tachycardia in 14 patients. Eight of the 32 patients had frequent and 10 had infrequent premature ventricular complexes. The initial QT_c in these three groups was 0.52 ± 0.007, 0.47 ± 0.03, and 0.46 ± 0.03, respectively. The occurrence of ventricular tachycardia also was associated with a higher peak serum enzyme level, suggestive of a more extensive infarction. However, the QT_c in the group with ventricular tachycardia shortened by the fifth day after infarction to the same extent as in the other groups (116). In two other studies of patients with acute myocardial infarction, there was no evidence that ventricular fibrillation was associated with a prolonged QT_c (117) or that a lengthening of QT_c by up to 20% more than the initial value was predictive of serious ventricular arrhythmias (118).

In a study (119) of 1,157 miscellaneous medical patients of whom 141 died, QT_c averaged 0.403 in survivors and 0.423 in nonsurvivors. Also, in that study (119), a prolonged QT_c (>0.44) occurred significantly more frequently in patients dying suddenly or dying after acute myocardial infarction than in victims of a noncardiac death. The study does not report whether QT_c in the victims of cardiac death was prolonged secondary to past myocardial infarction or whether drugs might have been involved.

Two prospective studies (120,121) suggest a possible long-term predictive value of QT_c lengthening. In one (120), 125 survivors of out of hospital ventricular fibrillation were compared with 98 ambulatory patients after myocardial infarction. In the survivors of ventricular fibrillation, QT_c was prolonged in 35%, averaging 0.426. In ambulatory patients after myocardial infarction, QT_c was prolonged (>0.44) in only 18% and averaged 0.412. In another study (121) of 55 survivors of myocardial infarction followed up for 7 years, the QT_c of 27 survivors averaged 0.429 and for the 28 deceased individuals 0.443 (121). This study does not provide information about other risk factors known to affect the prognosis in survivors of myocardial infarction, and no information about treatment with antiarrhythmic drugs that affect QT_c is available.

Vedin et al. (122) investigated 150 predictive variables in 292 survivors of myocardial infarction and QT_c, although studied, was not listed among the most prominent predictive variables. In the study of Ahnve et al. (123) QT_c measured at discharge in 463 patients with acute myocardial infarction had no relation to long-term prognosis. In that study (122),

Figure 7. Electrocardiograms from a 50 year old woman obtained on the same day before (**left**) and after (**right**) myocardial infarction. Note the prolongation of the QT interval. The coupling interval of the ventricular premature complex (in V_3 [**left**] and in both leads [**right**]) remains the same, but because of QT prolongation, an R on T phenomenon occurs after myocardial infarction.



a prolonged QT_c (>0.44) was present in 31% of patients but it was not associated with increased mortality. Also, in another study (124) of 91 survivors of myocardial infarction, QT_c measurement failed to identify high risk groups and there was no significant association between QT_c and the occurrence of complex ventricular arrhythmias. In yet another study (17) of 100 survivors of myocardial infarction of whom 20 died during the follow-up period, there was no significant difference in survival between persons with a normal and a prolonged QT_c. A tentative conclusion from the results of these studies is that even if the data are valid, QT_c has little, if any, predictive value either during the acute phase or during convalescence after myocardial infarction.

Mitral Valve Prolapse

The possible role of prolonged QT_c as a contributor to arrhythmias in patients with mitral valve prolapse has received increasing attention (references in reference 125). In two studies (126,127), QT_c prolongation (>0.43) was found in 29 of 40 patients (126) and in 44 of 94 patients (127). In another report (125), the average QT_c of 56 patients with mitral valve prolapse was 0.48 compared with 0.38 in 62 normal volunteers. In that study (125), a QT_c of 0.46 or longer occurred in 36 of 56 patients, and the QT_c lengthening was associated with a higher prevalence of ventricular arrhythmias. Also, it has been reported (128) that patients with symptomatic mitral valve prolapse exhibit exaggerated response to administered isoproterenol manifested by greater prolongation of the QT interval relative to the duration of mechanical systole (QS_2) than in subjects with asymptomatic mitral valve prolapse. In contrast to these reports are the results of the Framingham study (129) in which a QT_c greater than 0.44 was present in 5% of 208 subjects with and in 7% of 2,727 subjects without mitral valve prolapse. It is possible that the divergent results are related to the conditions of the patients at the time of the study.

The evidence that patients with mitral valve prolapse have a longer QT_c than subjects matched for age, sex and physical condition remains inconclusive. In addition, in the studies reporting QT_c prolongation, the prolongation is slight and seldom reaches values at which a long QT_c is linked with the appearance of torsade de pointes due to drug administration or the congenital long QT syndrome.

Miscellaneous Conditions

Lesser degrees of QT_c prolongation, (usually <115%) have been reported in a variety of conditions that include diabetes mellitus (130), chronic alcoholism (131), depression (132) and induction and maintenance of anesthesia (133,134). In most of these reports, the QT_c values are not abnormal, but are significantly longer than in the respective matched control groups. Variable QT_c prolongation can be also caused by accidental or induced hypothermia and several drugs outside the antiarrhythmic and psychotropic categories, for example, quinine (135), probucol (136), Atabrine and emetine (7).

Conclusions

Causes. Table 3 summarizes our conclusions about the relations between prolonged QT_c, the autonomic nervous system, dispersion of repolarization and propensity to ventricular arrhythmias. The congenital long QT syndrome appears to be the only apparently neurogenic disorder associated with an increased prevalence of ventricular tachycardia (torsade de pointes). That the arrhythmia is probably secondary to increased dispersion of ventricular repolarization is evidenced by studies of effective refractory period, monophasic action potential duration and the R on T phenomenon in these patients. The acquired neurogenic long QT interval seen with cerebrovascular accidents, particularly intracranial hemorrhage, seldom predisposes to ventricular tachycardia. Although an increased dispersion of repolarization in this condition is probably present, there are no supporting data of the type that have been provided for patients with the congenital long QT syndrome. The remaining causes of long QT_c are, with the possible exception of organophosphorus poisoning, not primarily of neurologic origin, and not all of these conditions are associated with an increased propensity to ventricular tachycardia. The absence of arrhythmogenic potential is, perhaps, due to an absence of increased dispersion of repolarization (as with hypocalcemia and steady state hypothermia) or due to the short duration of induced dispersion (for example, injection of contrast material into coronary arteries).

In patients with various types of structural heart disease, QT_c is frequently prolonged. However, QT_c prolongation is seldom as marked as in other conditions listed in Table 1, and a critical role for prolonged QT_c in the genesis of ventricular arrhythmias in these patients has not been established.

Role in ventricular arrhythmias. The congenital long QT syndrome has served as a model for the prevailing hypothesis that neurogenic disorders of the heart precipitate or facilitate arrhythmias through increased dispersion of repolarization. The significance of a prolonged QT interval would assume greater significance if QT lengthening represented a predictable manifestation of increased dispersion of repolarization, and if increased dispersion of repolarization constituted an independent risk factor for arrhythmias and cardiac death in patients with coronary artery disease, cardiomyopathy, mitral valve prolapse and other forms of heart disease. The significance of a prolonged QT is tempered when it is realized that the characteristic configuration of arrhythmias accompanying the congenital long QT syn-

drome, that is, torsade de pointes, also is present in patients with acquired prolongation of QT secondary to treatment with antiarrhythmic drugs, electrolyte imbalance, marked bradycardia and certain metabolic disturbances, but not in association with other types of acquired prolonged QT, that is, the cerebrovascular accident pattern.

Role of pharmacologic treatment. The inability to predict when prolongation of QT is beneficial and when it is potentially harmful exemplifies an important deficiency in our knowledge concerning the role of dispersion of repolarization in arrhythmogenesis and in the pharmacologic treatment of ventricular arrhythmias. Although torsade de pointes in the congenital long QT syndrome is probably related to increased dispersion of repolarization, it is not known whether this also is true for the occurrence of torsade de pointes in patients treated with antiarrhythmic drugs because the arrhythmias do not appear to be related to any critical dose of the drug or any critical degree of QT_c prolongation. It needs to be established whether certain individuals treated with these drugs are particularly susceptible to the drug-induced QT prolongation, and whether such susceptibility unmasks a latent form of the congenital long QT syndrome.

Implications. While it is clear that the significance of a prolonged QT interval depends on its accuracy as a reflector of the status of ventricular repolarization, as we trace the increased interest in the QT interval to a more general interest in the effects of the nervous system and antiarrhythmic drugs on the dispersion of ventricular repolarization and ventricular arrhythmias, we conclude that the number of unanswered questions still bars judgment as to when the long QT interval is good, bad or indifferent. If it can be accepted, however, that repolarization is complete at or near the end of the QT interval and the the QT interval is an indicator of the total duration of repolarization, in the absence of "silent repolarization," the interval between the onset of premature ventricular depolarization and the end of the T wave represents the minimal dispersion of ventricular repolarization (Fig. 3). This measurement might provide a basis for systematic studies of dispersion and arrhythmia propensity. It needs to be reiterated that the limited accuracy and reproducibility of QT measurements must always be taken into consideration.

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