Abstract

The electrocardiographic QT interval has been extensively studied in ischaemic heart disease. Recently, there has been increasing interest in the relationship between diabetes and QT abnormalities. QT prolongation and increased QTd have been shown to predict cardiac death in both type 1 and type 2 diabetes mellitus. Although there is general agreement that QT interval is affected by cardiac ischaemia, the effect of hyperglycaemia on QT measures is controversial. There are also problems surrounding QTd. First, there is controversy as to whether the measure has any physiological meaning; secondly, there is no universally accepted method of measurement and hence no consensus about the upper limit of normal. Nevertheless, several studies have shown increased QTd in diabetic patients suggesting that assessment of the QT interval could be a cost effective way of stratifying such patients according to cardiovascular risk so that aggressive treatment could be directed appropriately to improve outcome.

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Introduction

Patients with diabetes mellitus are at an increased risk of dying from cardiovascular diseases, the reason for which is not completely understood. Excess cardiovascular risk in this population persists even after normalisation for other conventional cardiovascular risk factors (hypertension, dyslipidaemia, physical inactivity, smoking) suggesting that there are other incompletely understood mechanisms which increase cardiovascular risk in diabetic patients. Ventricular instability, as manifested in QT abnormalities, might be an important additional mechanism.

What are QT abnormalities

The QT interval, which is easily obtained from a standard resting ECG, reflects the total duration of ventricular myocardial depolarisation and repolarisation. It can be corrected for heart rate by using a variety of formulae. The QTc effectively is the QT interval estimated at a rate of 60/minute. A commonly used correction formula is that of Bazett1 where QTc=QT/√RR interval. The Bazett formula, which has been heavily criticised, in fact gives a slight over correction of QT interval at higher heart rates while the formula of Hodges et al.2 (QTc=QT + 1.75 (rate - 60)) has been shown to perform much better and is gradually gaining more widespread acceptance.3 There are, however, very many QT correction formulae, a detailed discussion of which is beyond the scope of this article. QTc prolongation is a risk factor for sudden death independent of age.4 The relationship between prolonged QT interval and an increased risk of sudden death has been extensively studied in ischaemic heart disease5 and a relative risk of 2–5 has been reported. The long QT syndrome is associated with a very high risk of ventricular fibrillation6 and drugs such as quinidine that prolong the QT interval may also cause sudden arrhythmic death.

QTd is defined as the difference between the maximum and minimum QT interval on the 12 lead ECG (QTd = QT max - QT min). A single QT interval on the surface ECG does not give any information on dispersion of recovery time (i.e. repolarisation) but QTd is said to reflect spatial differences in myocardial recovery time.7 Healthy subjects exhibit a small degree of QTd.8 Increased QTd has been observed in chronic heart failure,9 peripheral vascular disease,10 hypertension,11 hypertrophic cardiomyopathy12 and in CHD,13 and has been correlated with increased risk of cardiovascular death in these conditions and in healthy subjects.14 Increased QTd after acute MI is a risk factor for sudden death and QTd has been shown to decrease after successful thrombolytic therapy.15 It is, therefore, believed that QTd following an acute MI depends not only on infarct site and size but also on reperfusion status.

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Increased QTd may indicate non-uniform ventricular repolarisation, thus possibly providing a substrate for the development of malignant ventricular arrhythmias. Endocardial monophasic action potential studies have demonstrated that there are regional differences in the duration of myocardial repolarisation that may be reflected in the surface ECG. Homogeneity of ventricular recovery time is believed to protect against arrhythmias.

QTd can be corrected for heart rate but it has been argued that this should not be done. In any event, with a linear correction formula, e.g. the Hodges et al., 1983 formula, there is no need for QTd rate correction, i.e. QTd is the same before and after correcting for rate with this formula. QTc > 440 ms (0.44s) is universally considered as prolonged, although there are small gender based differences. There is still some confusion about the upper limit of normal QTd. QTd > 80 ms (0.08s) is usually considered as abnormally prolonged. However, on the basis of a study of over 3,000 neonates, children and adults, an upper limit for normal QTd of 50 ms was suggested by Macfarlane et al.

The main problem with QT interval assessment is that there is no universally recognised standard method of analysis or of lead selection. It may not be possible to measure QT interval in every lead, and measurement may be less than precise. QT interval can be measured erroneously by misinterpreting either the beginning of the QRS complex or the end of the T wave. Methodology for determining QTd varies between studies. It can be measured manually, by digitisers, photocopy enlargement of an ECG, and by special computer software. There is an urgent need for standardisation of lead selection and method of measurement. The intra- and inter-observer reproducibility of QTd is low (and significantly lower than that of QT interval) and has been shown to vary and the results, therefore, may not be fully comparable between studies. Some authors have raised doubts about the meaning of QTd. It has been suggested that QTd is unlikely to reflect any aspect of myocardial repolarisation and that it results mainly from the variations in T loop morphology and QT measurement error.

Why QT in diabetes?
Recently there has been growing interest in the relationship between diabetes and QTc and QTd. Prevalence of prolonged QT interval and increased QTd is higher in people with type 1 and type 2 diabetes as compared to non-diabetic subjects, especially in the presence of autonomic neuropathy. The prevalence of QT prolongation has been reported to be as high as 16% in type 1 diabetes (11% in males and 21% in female patients) and 26% in type 2 diabetes, while that of increased QTd has been reported as 7% in type 1 diabetes (8% in men and 5% in women) and 33% in type 2 diabetes. No association between QT abnormalities and gender has been observed in type 2 diabetes. Diabetic patients with more pronounced QT abnormalities tend to have higher age and blood pressure and they tend to have cardiovascular complications. However, even patients with a recent diagnosis of diabetes and without overt cardiac complications have been observed to have increased QTd compared to non-diabetic subjects. QT interval is affected by CHD and autonomic neuropathy and it is possible that these new diabetic patients with prolonged QT interval and increased QTd may have had undiagnosed neuropathy or CHD.

Prolonged QTc and increased QTd are independent markers for CHD in type 1 and type 2 diabetes and have been demonstrated to be highly significant predictors of cardiac death even in newly diagnosed type 2 diabetes. Comparison between QTd and microalbuminuria suggests that increased QT dispersion is a better predictor of cardiac death in patients with diabetes. QTd > 78 ms after six years of diabetes predicted cardiac death with 100% sensitivity and 90% specificity i.e. an odds ratio of nine, compared with an odds ratio of 1.8 for microalbuminuria (95% CI, 1.2–2.8) in an overview.

No association has been found between QTd and microvascular diabetic complications.

**QT interval and autonomic neuropathy**
Cardiac autonomic neuropathy is a well-recognised complication of diabetes and is believed to be responsible for an increased risk of sudden death. Ewing’s battery of tests remains too cumbersome for use in routine clinical practice. Consensus statements released by the American Diabetic Association and the American Academy of Neurology indicate that testing for prolongation of Bazett’s heart rate-QTc is easy and specific for diabetic cardiac autonomic failure. QTc, however, is seldom used to evaluate alteration in cardiac sympathetic innervation in the clinical setting because of its insensitivity for autonomic failure. A meta-analysis recently concluded that measurement of QTc is a more accurate test for autonomic failure in young men with diabetes and that QTc rules out autonomic failure best among diabetic patients in whom it is most sensitive (i.e. men and young people). In a recent study among patients with type 1 diabetes, QTc did not correlate with the severity of autonomic neuropathy as indicated by other cardiovascular autonomic tests. Thus, there is general agreement that the presence of cardiac autonomic dysfunction increases the duration of the QT interval but it is still controversial as to whether or not it influences QTd. Most studies have failed to demonstrate any significant association between QTd and autonomic dysfunction in multivariate analysis.

**QT interval and hyperglycaemia in diabetes**
The reasons for QT abnormalities in diabetes are not complete-
ly understood. Does uncontrolled hyperglycaemia per se contribute to QT prolongation and increased QTd? In a study of healthy non-diabetic subjects, an independent association between high plasma glucose concentration and increased QTc duration and QTd was reported. It was further shown in the same study that inhibition of glucose induced insulin release, by octreotide infusion during a hyperglycaemic clamp, did not influence ECG changes, suggesting that insulin does not play a major role in glucose induced ECG changes. A similar relation was observed between QTc duration and fasting glucose in a large population based study of more than 6,500 patients. QT interval duration was found to be independently associated with HbA1C in type 1 diabetes in the EURODIAB IDDM Complication Study.

In several studies in type 1 diabetes and type 2 diabetes, QT abnormalities were not influenced by the level of metabolic control (HbA1C) or duration of diabetes. In another study, mean HbA1C was significantly greater for those with a QTc in the upper tertile compared to the lower tertile among adults with diabetes (8.0% vs. 7.5%, p<0.05) and impaired fasting glucose (5.7% vs. 5.4%, p<0.05), but there was no difference among adults with normal glucose. A possible influence of hyperglycaemia on QT abnormalities can not be excluded and is worthy of further research.

It has been proposed that hyperglycaemia may produce ventricular instability by increased sympathetic activity, increased cytosolic calcium content in myocytes or both. Insulin stimulates sympathetic activity and diabetes is known to be associated with impaired parasympathetic cardiac control. This is reflected in a reduced ability to regulate heart rate as well as a reduction in heart rate variability.

**QT interval and macrovascular risk in diabetes**

In the United Kingdom Prospective Diabetes Study (UKPDS), which enrolled adults with newly diagnosed type 2 diabetes, a significant reduction in all microvascular end points was noted in the intensive treatment group compared to the standard treatment group while a trend toward a reduction in cardiovascular outcomes was not statistically significant (p=0.052). However, it has been shown in an epidemiological analysis of a UKPDS cohort that, for every 1% reduction in HbA1C, there was an approximately 14% reduction of all cause mortality and MI, an effect which was statistically significant. A systematic review after analysing data from six randomised controlled trials comparing conventional treatment with intensive insulin therapy noted a moderate treatment effect of glycaemic control on macrovascular events in type 1 diabetes.

Improving metabolic control, including glycaemia, substantially reduces the burden of cardiovascular disease in diabetes.

The mechanism by which prolonged QT interval and increased QTd predict increased cardiac mortality and morbidity in diabetes has been much debated. It appears that these two parameters provide different information. QTd is believed to correlate to a greater extent with the risk of ventricular arrhythmias than QT prolongation. Some conditions associated with a prolonged QT interval, e.g. therapy with sotalol may actually reduce the risk of sudden death in association with a reduction in QTd but an increase in QTc. It was initially thought that this is because QTd reflects electrical heterogeneity, but this view has now been challenged and QTd has been proposed as a non-invasive marker of potentially lethal underlying cardiac abnormalities – the most important being ischaemia. It is further supported by the observation that QTd is prolonged immediately after an MI and tends to reduce after successful thrombolysis. Overall, increased QTd seems to represent the sum of several adverse cardiac abnormalities such as fibrosis, hypertrophy, dilatation, ischaemia and probably, autonomic dysfunction. All these factors individually confer increased cardiovascular risk and QTd, as a summation, could be a global prognostic marker for cardiac mortality in patients with diabetes. The debate on what causes sudden death – arrhythmia or ischaemia – continues. It has been suggested that a patient with QT abnormalities should undergo tests for myocardial ischaemia (treadmill test) as well as left ventricular abnormalities (echocardiogram).

### Further directions

Most of the studies of QT abnormalities in diabetes are observational and there is a marked paucity of interventional studies. There is a wealth of data to link QT abnormalities with cardiac ischaemia, but these abnormalities have been found even in newly diagnosed diabetic patients with no apparent cardiac disease. Despite an extensive literature search, no study was found that has assessed the effect, if any, of controlling hyperglycaemia on QTd and QT prolongation in patients with diabetes. It will be of interest to know if these QT abnormalities can be ameliorated by successful control of hyperglycaemia in diabetic patients without cardiovascular complications. However, improved glycaemic control will need to be achieved by diet or by drugs that do not by themselves affect QT interval (e.g. metformin, insulin). It has been recently shown in a small study that glibenclamide, a commonly used second-generation sulphonylurea, causes an increased QTc and QTd. However, larger studies are needed to clarify this further.

Increased QTd could possibly be used to identify a subgroup of diabetic patients which is at a particularly high risk of adverse cardiovascular outcome. Patients with this QT abnormality could be targeted for more detailed cardiac investigations, including a treadmill test, echocardiogram and angiography. If other structural or functional cardiac abnormalities are identified, specific therapeutic efforts, e.g. aggressive lowering of blood pressure etc. may be undertaken in an attempt to alter the outcome favourably.

Despite the problems inherent in the accuracy and reproducibility of QT measurements, the greatest advantage of using the QT interval as a screening test is that it does not require patient compliance, is non-invasive, easily obtained and cost effective.

However, it remains to be seen if more aggressive control of hyperglycaemia in this subgroup will help in improving QT...
abnormalities (i.e. ventricular instability) and, therefore, cardiac outcome. More long-term interventional studies are needed to shed light on this issue.

References
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