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Review

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QT dispersion in medicine: electrophysiological Holy Grail or fool's gold?

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Introduction

If subjects at high risk of sudden cardiac death were easily identifiable, then targeted therapy might be able to reduce cardiac deaths. Unfortunately, we do not yet possess an applicable screening method for this purpose. Techniques exist for this such as signal-averaged electrocardiography (ECG), T-wave alternans and heart rate variability, but they have variable success and tend to require specialized equipment, making them difficult in routine practice. Another possibility is QT interval analysis, which stems from the fact that individuals with long QT syndromes are known to be at high risk of sudden cardiac death. Taking this principle one step further, it is possible that the variation of QT intervals within an ECG in more routine patients may also contain prognostic information. 'QT interval dispersion' is at present undergoing vigorous assessment for this purpose. Several years ago, Campbell *et al.*[1] enthusiastically called it the 'electrophysiological Holy Grail'. The number of studies indexed in the Medline on QT dispersion has risen 34-fold since its description in 1990. There is therefore a need to synthesize this information and discuss whether this technique could be adopted in clinical practice.

Development and physiological basis of QT dispersion

A Dutch physician, Willem Einthoven (1860–1927) introduced the ECG 'PQRST' designations we use today, and the 'QT interval' has been known since 1887 to represent ventricular electrical activities.[2] One hundred years later, a group from Newcastle[3] proposed that the interlead QT interval differences within a 12-lead ECG might reflect regional differences in myocardial refractoriness, and that this might predict cardiac dysrhythmias. Animal[4] and human[5] studies supported this observation. Using epicardial monophasic action potentials in isolated rabbit hearts, Zabel *et al.*[6] correlated this QT interval variation with the degree of homogeneity in ventricular repolarization. This correlation would suggest that QT dispersion is at best a surrogate marker, rather than an accurate measure of ventricular repolarization. In reality, the repolarization process is nondipolar, and hence there is only one end-of-repolarization (where?) and the onset of repolarization is nearer to the T-wave peak within a surface ECG (see below).[7]

Methodological issues

QT dispersion measurement

QT dispersion is simply defined as the difference between the longest (QTmax) and the shortest (QTmin) QT intervals within a 12-lead ECG. As far as possible, each of the twelve QT intervals should be individually measured to determine the values of these two extreme indices. Since the QT interval on its own may vary according to the heart rate, it may

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be corrected using Bazett's formula to give rise to QTc intervals, and the difference between QTcmax and QTcmin is the QTc dispersion.

In measuring a QT interval, the beginning of the Q-wave is easily identifiable, as is the end of the T-wave under normal circumstances. Difficulties arise when the morphology of the T-wave is abnormal, or when a U-wave is present. This has led to differing definitions of T-wave measurement, causing some confusion. Thus, the end of the T-wave has been variously defined as at the intersection of an extrapolated line of the downward slope to the isoelectric line, at the return of the T-wave to the isoelectric line, and the nadir between the T- and U-waves. Nonetheless, the latter two T-wave end-definitions are most commonly used in practice. The T-end interval, the interval between T-wave peak to its end,[8] and the JT interval, or the difference between QT interval and QRS duration, have been suggested as alternatives to the QT interval, but these measurements do not overcome the controversy of T-wave end definition. The QaT interval, or the interval between the Q-wave and the T-wave peak, is obviously attractive as it precludes the need to define where the T-wave should end. However, this measurement lacks the prognostic value established on the QT interval dispersion.

Lead correction

A dilemma arises when the QT intervals are not measurable in all 12 leads, and it is not possible to tell whether any of the omitted leads contain the extreme QT values necessary for QT dispersion. To overcome this problem, Day *et al.*[9] proposed that this bias might be correctable by dividing the resulting QT dispersion by the square root of the number of missing leads, and that a minimum of six leads should be measurable. Another suggestion was to assess only a set of standardized leads,[10] instead of correcting for random lead adjustment. Some investigators[11,12] suggest that some leads are more likely to contain the extreme QT values, and if omitted, will significantly affect the resulting QT dispersion. It is still unresolved whether the chest leads reflect electrical differences more closely than the limb leads.[13] The current consensus is to use only ECGs with at least eight measurable leads, bearing in mind that only two limb leads are necessary to mathematically derive the other four limb leads.[14] Missing lead correction has not gained wide acceptance, but further studies are required to settle this issue.

Paper speed

QT interval measurements are more reproducible with faster paper speed recordings.[15] Conversely, QT interval lengthens with slower paper speeds, as well as the ECG gain and hence the T-wave amplitude.[16] It is uncertain how to strike a fine balance, but most studies used a paper speed of 25 mm/s, at a speed the standard 12-lead ECG is recorded in clinical practice.

Heart rate correction

Bazett's formula[17] $QTc = QT/\sqrt{(RR)}$, which was described about eight decades ago, is most widely used for QT interval heart-rate correction. More recently however, the validity of this formula has come into question.[18,19] Some[20,21] have argued that the fact that QTc following heart rate correction still correlates with the heart rate suggest that this formula does not fully correct for the heart rate, but provided that the heart rate is <100 beats/min, this formula is generally acceptable. This is because there is a tendency for this formula to overcorrect at higher heart rates.[22] An alternative linear correction formula has been suggested[23] for correction, especially for higher heart rates. More and more researchers are now abandoning the need to correct QT dispersion for heart rate.[11,24,25] Perhaps heart rate correction is more relevant when individual QT intervals are compared, in particular the QTcmax, which in itself has prognostic value.[26] Despite this controversy, several studies[27] including the Rotterdam study[14] (see below) compared five commonly applied correction methods. All gave similar results, and this included Bazett's formula. A recently proposed QT interval correction on an individual basis based on exercise-induced heart rate changes holds promise.[22]

Reproducibility

The major problem with the manual measurement of QT intervals using an electronic digitizing pad is the poor inter-observer reproducibility, making comparisons between centres invalid. In one study,[11] the inter-observer relative error for QT dispersion was reported to be as high as 25–35%. This limitation may be overcome with automated systems of the future, however. In the meantime, research is mainly done with all measurements made by a single observer, as intra-observer reproducibility is generally good. The issue of reproducibility needs to be fully addressed before QT dispersion is ever likely to enter clinical practice.[20]

Population studies of QT dispersion

What constitutes a normal level of QT dispersion is still being debated. The average normal value of QT dispersion in normal subjects was $\leqslant 40$ ms in 13 studies and $\geqslant 40$ ms in eight studies.[28] Perhaps the QT dispersion in normal subjects should be

$\leqslant$50 ms.[20] In the large Rotterdam study[14] ($n=5812$), apparently healthy older subjects aged $\geqslant$55 years followed up over a mean period of 4 years with QTc dispersion $>$60 ms (vs. $<$39 ms) had a two-fold increase in sudden cardiac death. The prognostic value of QTc dispersion in this study was similar to that of ECG left ventricular hypertrophy (LVH) in predicting cardiac death. Another study from Denmark ($n=3455$) involving subjects aged 30–60 years followed up over 13 years, reported that QT dispersion $\geqslant$80 ms when compared with $<$30 ms (or QTc dispersion $\geqslant$90 ms vs. $<$40 ms) independently predicted a four-fold rise in cardiac death.[29] A further population-based study involving over 3000 adults and children suggested that QT dispersion $\leqslant$50 ms indicated normality; age or gender having no impact on this definition.[13]

Clinical applications of QT dispersion

Hypertension

One quarter of the adult population has hypertension, and sudden cardiac death is prevalent in this population.[30] The presence of LVH suggests poor prognosis, and is predictive of this adverse outcome.[31,32] Interestingly, QT dispersion relates to the resting systolic, but not the diastolic blood pressure, and is increased in LVH.[33,34] Galinier *et al.*[35] reported a follow-up study of 214 apparently healthy hypertensives where 1 in 20 died suddenly over a 2-year period. Patients with QT dispersion $>$80 ms were five times more likely to suffer this fate. Attempts have thus been made to assess the effects of antihypertensive agents on QT dispersion.[36–38] ACE inhibitors[37] on their own, or in combination with calcium channel blockers,[38,39] and the new angiotensin II receptor blocker, irbesartan,[40] have all been shown to reduce QT dispersion. The last study was the only randomized controlled trial to date, and also the first to demonstrate a relationship between the change in systolic blood pressure with treatment and the reduction in QT dispersion. This finding may not be surprising, as we have further demonstrated that experimental blood pressure elevation with phenylephrine infusion in normal human volunteers increases QT dispersion independently of heart rate changes.[41] It has not been established whether the reduction in QT dispersion with treatment relates to LVH regression[38,39] and whether this is paralleled by an improved outcome.

Ischaemic heart disease

QT dispersion predicts ischaemia-related cardiac dysrhythmias in patients with ischaemic heart disease.[42] Under controlled circumstances where myocardial ischaemia is induced using atrial pacing, QT dispersion increases only in subjects with significant coronary heart disease, and not in normal controls.[43,44] Our group have extended this observation, and reported that a QT dispersion rise of $<$16 ms during exercise has a 95% negative predictive value in excluding significant coronary artery disease.[45] In women, where routine exercise ECG is associated with a high rate of false positives, adding an extra criterion of having a QT dispersion during exercise $>$60 ms to ST-segment depression increases the specificity for coronary heart disease to 100%.[46] Interestingly, beta-blockade blunts exercise-related QT dispersion increase in subjects with ischaemic heart disease.[3,47] Thus, exercise QT dispersion may be a valid additional diagnostic criterion only if drugs are withdrawn, and should be interpreted with caution when concurrent drug administration occurs. This is an area of great interest with obvious important clinical implications; how best to measure QT dispersion, and how anti-anginal drugs affect this index during exercise.

Myocardial infarction

Myocardial infarction is a difficult area in which to measure QT dispersion, because the ECG is abnormal and changing rapidly. It is unclear when best to measure QT dispersion following acute myocardial infarction (AMI). The labile nature of QT dispersion during AMI has been well documented.[48] At least one study[49] reported that QT dispersion measured 2–3 days following an AMI was of no long-term prognostic value. Delaying this measurement to 4 weeks later, however, does help although it is still not very useful.[50,51] Some studies[8,13,15,51–53] report that an increased QT dispersion post-AMI predicted ventricular fibrillation, although the subject numbers in these studies were generally small.

However, it is possible that changes in QT dispersion over time *within* an individual give useful information. During AMI, a fall in QT dispersion occurs following successful thrombolysis,[54–56] with a parallel reduction in arrhythmic risk, although these findings are not universal.[57–59] Successful revascularization, as evidenced by positron emission tomography indicating myocardial viability, relates to a reduction in QT dispersion.[60] Similar findings have been reported with successful coronary angioplasty.[61,62] Interestingly, QT dispersion increases in response to restenosis following coronary angioplasty,[62] with a subsequent reduction of this index following repeat intervention. QT dispersion may thus be a useful index to assess procedural success. Also, QT dispersion may help to identify patients with chest pain who are at risk of AMI.[63]

Heart failure

Seventy-five percent of patients with congestive heart failure (CHF) eventually suffer sudden cardiac death.[64] The precipitating event in most cases is likely to be cardiac dysrhythmia, and this relates to left ventricular function.[65] Thus, QT dispersion, being an index of cardiac dysrhythmia, may be useful as a prognostic guide. Although we reported a link between QT dispersion and sudden death in CHF[66] and others confirmed this finding,[67,68] not all studies agree.[50,69–71] It is worth commenting that these variable results in CHF may be because CHF patients have very abnormal ECGs, and this worsens the methodological problems in measuring QT dispersion.

However, as with MI patients described above, changes in QT dispersion *within* an individual may give more meaningful information. It is at least intriguing that the three treatments which improve mortality in CHF (ACE inhibitors, beta blockers and spironolactone) all improve QT dispersion within individuals.[72,73]

Diabetes

Diabetes is a very potent risk factor for cardiovascular disease.[74,75] This risk is multiplied in the presence of other factors such as microalbuminuria,[76] hypertension,[77] smoking,[78] and hyperlipidaemia.[79] For these reasons, the diabetic population also has a high incidence of sudden deaths, and QT dispersion does predict this outcome.[26,80,81] This is true for both types of diabetes, insulin-dependent or not.[82,83] The study we have reported[26] ascribed a very high predictive value of increased QT dispersion >78 ms in predicting cardiac death with 100% sensitivity and 90% specificity (odds ratio 9.0) in 182 patients with non-insulin-dependent diabetes followed up for a mean period of 10.3 years. In comparison, microalbuminuria had an odds ratio of 1.8 in predicting cardiac death in the same study. Others have confirmed our findings.[80] QT dispersion may have performed particularly well in diabetics because their ECGs tend to be much more normal than CHF or MI patients.

Other common diseases

QT dispersion $\geqslant 60$ ms (92% sensitivity, 81% specificity) predicts cardiac death in patients with peripheral vascular disease in the absence of overt ischaemic heart disease. Patients on the cardiac transplant waiting list with a raised QT dispersion (>120 ms) have a 4.5-fold increase in mortality prior to transplantation.[84] Patients with mitral valve prolapse have increased QT dispersion, and this may explain why ventricular dysrhythmias are prevalent in this group of subjects.[85,86] In addition, increases in QT and QTc dispersion have been reported in patients with systemic sclerosis,[87] rheumatoid arthritis,[88] and Behçet's disease.[89]

Athletes with symptomatic ventricular tachycardia have increased QT dispersion.[90] Hence, this simple technique may be useful as a test in sports to identify individuals at-risk of sudden cardiac death, including those with undiagnosed hypertrophic obstructive cardiomyopathy.[91–94] This method of screening however has not been tested systematically. More recently, increased QT dispersion has been demonstrated in patients with Duchenne muscular dystrophy[95] and chronic obstructive pulmonary disease.[96]

Limitations

QT dispersion can only be measured in good-quality ECG recordings, and this also excludes patients with bundle branch block, atrial flutter/fibrillation, and patients with pacemakers *in situ* who are probably at risk of cardiac death. Also, to date, most reported studies are observational and retrospective in nature. There have not been any prospective interventional studies to assess whether increased QT dispersion is a modifiable risk factor with the potential to alter outcome, as has been demonstrated with blood pressure and cholesterol lowering.

Conclusions

Over the past 10 years, QT dispersion as a measure of cardiac electrical heterogeneity has been shown to be of prognostic value in many common medical conditions. However, there are genuine methodological difficulties in measuring QT intervals in ECGs which are frankly abnormal. For this reason, QT dispersion is of less value to cardiologists, whose patients nearly always have very abnormal ECGs. QT dispersion is of much more value in patients with less overt cardiac disease and more normal ECGs, for example in patients with diabetes, peripheral vascular disease, transient ischaemic attacks, hypertension, etc. Such patients are more likely to be seen by physicians than cardiologists.

Few tests are ever useful in every clinical situation, and it would be our prediction that QT dispersion will establish itself in populations of patients with normal or mildly abnormal ECGs but not in patients with very abnormal ECGs to start with. Another use for QT dispersion could be to shed light on the mechanisms of cardiac death, i.e. if we can establish what spectrum of cardiac abnormalities are over-represented in patients with raised QT dispersion, then we will also be establishing which cardiac abnormalities are most associated with a later cardiac

death. Once we know this, we will be able to see how reversible (or not) these abnormalities are likely to be.

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