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Sensitivity and specificity of QTc dispersion for identification of risk of cardiac death in patients with peripheral vascular disease

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Abstract

***Objective*—To determine whether QTc dispersion, which is easily obtained from a standard electrocardiogram, can predict those patients with peripheral vascular disease who will subsequently suffer a cardiac death, despite having no cardiac symptoms or signs.**

***Design*—Patients with peripheral vascular disease were followed up for five years after they had had coronary angiography, radionuclide ventriculography, and their QTc dispersion calculated from their 12 lead electrocardiogram.**

***Subjects*—49 such patients were then divided into three groups: survivors (34), cardiac death (12), and non-cardiac death (3).**

***Main outcome measure*—Survival.**

***Results*—The mean (SD; range) ejection fractions were similar in all three groups: survivors 45·9 (11·0; 27·0-52·0), cardiac death 44·0 (7·90; 28·5-59·0), and non-cardiac death 45·3 (4·55; 39·0-50·0). QTc dispersion was significantly prolonged in the cardiac death group compared with in the survivors (86·3 (23·9; 41·0-139) v 56·5 (25·4; 25·0-164); P=0·002). A QTc dispersion ⩾60 ms had a 92% sensitivity and 81% specificity in predicting cardiac death. QTc dispersion in patients with diffuse coronary artery disease was significantly (P<0·05) greater than in those with no disease or disease affecting one, two, or three vessels.**

***Conclusions*—There is a strong link between QTc dispersion and cardiac death in patients with peripheral vascular disease. QTc dispersion may therefore be a cheap and non-invasive way of assessing the risk of cardiac death in patients with peripheral vascular disease.**

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Introduction

Patients with peripheral vascular disease commonly have coronary artery disease, which is asymptomatic in most cases. Despite being free of symptoms, these patients are at high risk of dying from cardiac causes. It would therefore be worth while to identify patients at most risk of cardiac death so that they could receive appropriate cardiac treatments, in addition to treatment for vascular disease.[1]

A fairly new and simple variable currently under investigation in cardiac disease is QT dispersion.[2] Here the QT interval is calculated for all 12 electrocardiographic leads, and the shortest interval is subtracted from the longest interval to give the QTc dispersion. We have shown recently that QTc dispersion was prolonged in patients with chronic heart failure who died suddenly and unexpectedly as compared with a group of such patients who were matched for severity of disease but who survived.[3] Similar data linking QTc dispersion and cardiac death also exist for patients after myocardial infarction and for patients with hypertrophic cardiomyopathy.[4,5]

We therefore investigated whether in patients with

peripheral vascular disease QTc dispersion is able to predict those who are at increased risk of cardiac death.

Patients and methods

The study comprised 49 patients (mean age 62 (range 47-76) years) referred for the first time to the vascular clinic for intermittent claudication. Consecutive patients with intermittent claudication but no clinically obvious cardiac disease were selected for study in 1986-7. The original purpose was to assess coronary arteriographic findings in a group of patients with peripheral vascular disease and no cardiac disease, but these data were not published at that time. The lack of obvious cardiac disease was based on the fact that they had no symptoms whatever of coronary artery disease and no electrocardiographic signs of ventricular hypertrophy, ischaemia, or previous myocardial infarctions—that is, no ST segment depression or elevation and no pathological Q waves. T wave inversion was allowable but was present in only five patients (four survivors and one cardiac death). No patients were taking antiarrhythmic drugs that could affect the QT interval. The number of patients recruited was purely arbitrary and was based on the workload generated, the time available to the researchers, and the invasive nature of the coronary angiography. Consecutive patients with intermittent claudication who were not included were those with symptoms of coronary disease or electrocardiographic evidence of pathological Q waves or ST segment depression, or both. The patients were investigated intensively at enrolment (see below). It later occurred to us that these patients represented a well characterised group of patients in whom prognostic features could be determined and, in particular, whether QTc dispersion at baseline influenced survival. Therefore after a mean (range) of 66 (52-77) months the end points of survival and cardiac and non-cardiac deaths were assessed. The study was approved by the Tayside committee on medical research ethics.

ANALYSES OF QT INTERVAL

QT intervals from 12 lead electrocardiograms taken at enrolment in the study in 1986-7 were analysed. Three observers (DD, JL, and Dr Simonetta Dell'Orto), all unaware of the diagnoses or survival of the patients, independently measured QT intervals in all leads, if possible. All values presented in this paper represent the mean for all three observers. On a surface 12 lead electrocardiogram (25 mm/s speed), the QT interval was taken from the onset of the QRS to the end of the T wave—that is, return to the T/P baseline. If U waves were present the QT interval was measured to the nadir of the curve between the T and U waves. Three consecutive cycles were measured for each lead. QT intervals were corrected with Bazett's formula ($QTc=QT/RR^{1/2}$). QTc dispersion, defined as the difference between maximum and minimum QTc, was calculated from the electrocardiograms.

QT interval cannot always be reliably measured in every lead, and Higham and Campbell have pointed out that an observer should omit measurements in a lead if there is uncertainty rather than force a QT measurement which could well create a spurious QTc max or QTc min.[2] A standard way to attempt to compensate for this is to estimate the adjusted QTc dispersion, which is the measured QTc dispersion divided by the square root of the number of leads with analysable QT intervals.[2] In our study 84% of electrocardiograms had 11 or 12 leads measurable and 16% had nine or 10 measurable leads; no electrocardiogram had fewer than nine measurable leads. We also calculated the standard deviation of the QTc for each electrocardiogram: this is a way of minimising undue influence from one rogue lead. The coefficient of variation within individual patients for QTc dispersion was 4%-8%. The coefficient of variation between individual patients was 12%-18%.

RADIONUCLIDE VENTRICULOGRAPHY

The left ventricular ejection fraction was measured in 1986-7 by multiple gated acquisition radionuclide ventriculography with red blood cells labelled with technetium-99m. Imaging was done in a left anterior oblique position with a Starcam XC/T camera (General Electric). A normal value for the left ventricular ejection fraction in our hospital is 50%-55%.

CORONARY ANGIOGRAPHY

Our original purpose was to investigate the incidence of coronary artery disease by coronary angiography in patients with peripheral vascular disease who had no apparent cardiac disease. This is why coronary angiography was performed in these asymptomatic patients. The number of patients was relatively low because of the invasive nature of coronary angiography. These data, however, were not published in 1986-7. Clearly, these unpublished data became valuable when we later wished to see whether QTc dispersion would predict death.

Therefore coronary angiography was performed in 1986-7 through the femoral artery with the Judkins's technique. A coronary lesion was considered to be haemodynamically relevant if there was occlusion or a stenosis $\geq 50\%$ in diameter. Diffuse coronary artery disease was defined by the presence of generalised narrowing of all the major coronary arteries but no single stenosis or occlusion $\geq 50\%$ in diameter. All angiographic data were assessed independently by an experienced consultant cardiologist (GMcN).

PERIPHERAL VASCULAR DISEASE

Peripheral vascular disease was diagnosed by history, a resting ankle-branchial pressure index of $<0{\cdot}8$, and a drop in ankle systolic blood pressure of >30 mm Hg after a standard one minute exercise test.

MORTALITY

Five years after the first patient was enrolled the fate of the 49 patients with vascular disease was determined. In the 12 patients diagnosed as having a cardiac death, half died in hospital. The classification of the death as cardiac was based on one or more of the following features: five were described as sudden deaths in the case notes, three had postmortem examinations that showed evidence of a cardiovascular death, and in the three other cases myocardial infarction was the primary cause on the death certificate. In the six deaths out of hospital classified as cardiac the general practitioner confirmed that a sudden cardiac death had occurred, which was corroborated by telephoning relatives, who described the death as sudden—that is, <1 hour after onset of symptoms. In total therefore, 11 of these deaths were sudden. It is impossible to be categorical that all were definitely cardiac deaths, but we consider that we have been as rigorous as is ever possible in attributing precise causes of death. Even postmortem examination would have contributed little more, especially as we know that all who seemed to have had a cardiac death had coronary artery disease on previous angiography. Angiographic evidence before death makes the cause of death more robust in this study than in almost any other study.

In the group classified as non-cardiac death, postmortem evidence of widespread carcinoma was found in two of the three patients; the cause of death in the last patient was unknown but there was no evidence of cardiac causes.

STATISTICAL METHODS

We used one way analysis of variance to test for overall differences among the groups, followed by Duncan's range test to compare the separate group means when the F ratio was significant. Residuals for each variable were plotted and gave good agreement with normal distribution. For each of the separate group means, the SD and the minimum and maximum values (range) were also calculated.

Table 1—*Details of patients' treatment and concomitant diseases. Values are numbers of patients in each group*

Detail	Survived (n=34)	Cardiac death (n=12)	Non-cardiac death (n=3)
Drug treatment at entry:			
Dipyridamole	26	6	2
Diuretics	7	1	
β Blockers	5	2	
Calcium antagonist	2		
Hypoglycaemic drugs	2		
Concomitant disease at entry:			
Smokers	29	9	3
Hypercholesterolaemia	20	5	
Hypertension	5	6	
Diabetes	5	4	
Ischaemic heart disease events during follow up:			
Myocardial infarction	5	4	
Angina	7	4	
Treatment for peripheral vascular disease:			
Conservative	8	4	2
Grafting:			
Aortofemoral	4		
Iliac-femoral	1		
Femoropopliteal	11	5	
Angioplasty	8		1
Sympathectomy	2	2	
Amputation		1	

Table 2—*Characteristics of patients and angiographic findings*

Characteristicl	Survivors (n=34)	Cardiac death (n=12)	Non-cardiac death (n=3)
Mean (SD; range) age (years)	60·2 (7·58; 44·6-72·3)	65·3 (7·52; 51·6-77·0)	63·6 (4·14; 58·9-66·3)
No of men/women	19/15	8/4	2/1
Mean (SD; range) left ventricular ejection fraction (%)	45·9 (11·0; 27·0-52·0)	44·0 (7·90; 28·5-59·0)	45·3 (4·55; 39·0-50·0)
Mean (SD; range) ankle brachial pressure index	0·68 (0·19; 0·49-0·85)	0·62 (0·29; 0·08-0·85)	0·51 (0·10; 0·40-0·58)
Coronary angiography			
No with normal results	9		2
No with coronary artery disease			
1 Vessel	9	2	1
2 Vessel	4	2	
3 Vessel	3	4	
Diffuse	3	3	

Results

Table 1 shows details of the patients, their treatments, and their concomitant disease. Among those who died of cardiac causes hypertension and diabetes were more common and hypercholesterolaemia and smoking less common than in survivors—that is, the traditional risk factors did not help to discriminate survivors from non-survivors. These patients did not have coronary angioplasty, and only one of them subsequently had coronary artery surgery.

Patients who died of cardiac causes were clinically indistinguishable from those who survived in terms of the other traditional risk factors of age, left ventricular ejection fraction, or ankle brachial pressure index (table 2). In seven patients severe occlusive disease of the legs made cannulation of the femoral artery impossible. Coronary angiography showed a non-significant trend for increased cardiac death in those with diffuse coronary disease and triple vessel coronary disease.

Our most important finding was that patients who died from a cardiac cause could be readily identified by their QTc dispersion. This was true for the QTc dispersion itself, for the adjusted QTc dispersion, and for the standard deviation of the QTc dispersion so that we can have confidence that this relation was not due to forced QT measurements in unsuitable leads. Those who died from a cardiac cause had a significantly greater QTc dispersion than those who died from non-cardiac causes or who survived (table 3). Figure 1 and table 4 show the receiver operating characteristic curve for the link between QTc dispersion values and cardiac death. A QTc dispersion of 60 ms had a 92% sensitivity and an 81% specificity in predicting cardiac death during follow up, despite the fact that none of the patients had cardiac symptoms at the outset.

Figure 2 shows representative examples of two reasonably normal electrocardiograms with very different values for QTc dispersion. We found virtually the same with the standard deviation of the QTc dispersion as it was also significantly greater in those with cardiac death than in survivors. In fact, a standard deviation of ≥ 22 ms$^{1/2}$ had a 92% sensitivity and an 88% specificity at predicting cardiac death. On the one hand, the standard deviation of the QTc dispersion may be better than QTc dispersion in that it prevents isolated leads from having an undue influence, but, on the other hand, isolated leads with long QT intervals may be of arrhythmogenic significance and they would be better reflected by QTc

Table 3—*QTc dispersion and correlation with angiographic data. Figures are means (SDs; ranges)*

Detail	QTc (ms$^{1/2}$)			
	Maximum	Dispersion	Adjusted dispersion*	Standard deviation
Survivors (n=34)	440 (30·4; 384-546)	56·5 (25·4; 25·0-164)	16·7 (8·20; 7·44-54·1)	18·0 (6·48; 7·28-42·0)
Cardiac death (n=12)	473 (40·6†; 433-569)	86·3 (23·9†; 41·0-139)	26·7 (8·80†; 11·8-46·2)	29·3 (9·01†; 16·9-52·2)
Non-cardiac death (n=3)	441 (10·5; 430-451)	50·3 (13·6; 42·0-66·0)	13·8 (3·52; 11·3-17·8)	16·5 (4·25; 11·8-19·9)
Coronary angiography				
Normal results	437 (18·3; 384-473)	53·3 (14·5; 37·0-93·0)	15·7 (4·08; 10·8-26·9)	17·4 (4·72; 9·23-27·9)
Coronary artery disease				
1 Vessel	431 (17·0; 402-451)	51·4 (13·5; 41·0-81·0)	14·7 (3·93; 11·3-23·5)	17·6 (3·38; 12·0-23·2)
2 Vessel	461 (45·1; 410-546)	70·6 (43·5; 25·0-164)	21·3 (15·1; 7·44-54·1)	21·4 (11·0; 7·28-42·0)
3 Vessel	443 (39·8; 390-482)	78·3 (22·3; 46·0-97·0)	23·0 (6·57; 13·7-29·0)	23·3 (8·17; 11·8-29·8)
Diffuse	518 (45·5‡; 483-569)	120 (16·8‡; 109-139)	37·1 (7·99‡; 31·3-46·2)	39·6 (11·2†; 30·9-52·2)

*Adjusted for number of measurable leads.
†$P < 0.05$ for comparison with survivors or with deaths from non-cardiac causes.
‡$P < 0.05$ for comparison with normal results on coronary angiography or for one, two, or three vessel coronary artery disease.

dispersion itself. In this paper we are not trying to differentiate here between these two ways of measuring QT interval variability. Patients with diffuse coronary artery disease had a significantly greater QTc dispersion than patients without coronary artery disease or with disease affecting one, two, or three vessels (table 3). When it comes to predicting cardiac death there was no significant correlation between cardiac death and coronary angiographic findings. When the data are looked at in a different way, the finding of triple vessel disease had only a 36% sensitivity in predicting cardiac death, the sensitivity increasing to only 64% when the presence of either triple vessel disease or diffuse coronary disease was used as a predictor.

Table 4—*Sensitivities and specificities for predicting cardiac death at various cut off values for QTc dispersion (used for constructing receiver operating characteristic curve)*

Cut off point (ms) for QTc dispersion	Sensitivity (%)	Specificity (%)
≥163	0	100
≥130	8	97
≥100	17	95
≥90	33	95
≥80	67	89
≥70	83	89
≥60	92	81
≥50	92	43
≥40	100	8

Discussion

Our main finding was that QTc dispersion has a high sensitivity and specificity for identifying patients with peripheral vascular disease and no obvious disease who then suffer a cardiac death. This finding needs to be confirmed, but it could have enormous clinical utility because QTc dispersion is easily obtained, quickly and cheaply, from a non-invasive routine test. This contrasts with most developments in modern medicine, which usually require expensive and invasive technologies.

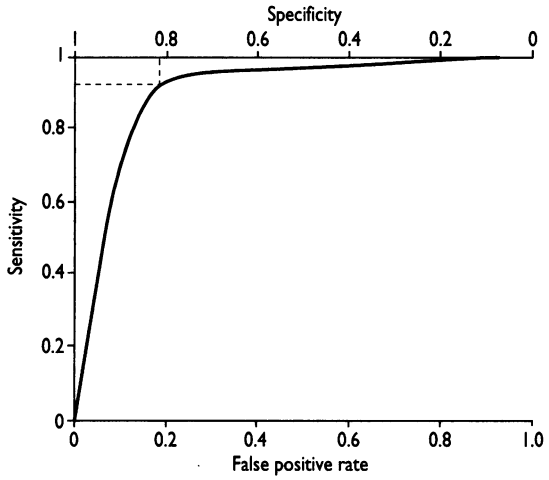

Fig 1—*Receiver operating characteristic curve for ability of QTc dispersion to predict cardiac death. Dotted line refers to cut off point of QTc dispersion of ≥=60 ms*

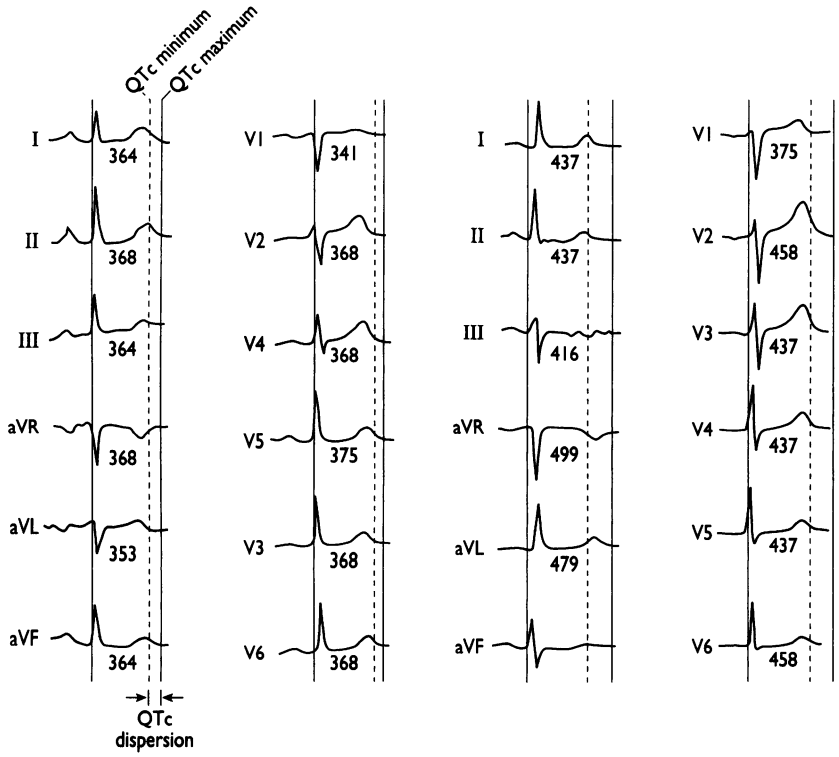

Fig 2—*Representative electrocardiograms to show how two reasonably normal tracings can have very different values for QTc dispersion*

The methodology of calculating QTc dispersion has not yet been clarified.[6] Nearly all current studies with QTc dispersion have entailed manual measurement, although digitising pads and automated methods are being developed, but neither new method has yet been validated. The relative error for QTc dispersion has been quoted at its worst as 25%-35%.[7] In this and most other studies, however, the differences in QTc dispersion between the groups are much greater than the errors in their measurement. For example, in this study those who died had a mean QTc dispersion which was 153% that of those who survived, which makes reproducibility problems less crucial. The fact that the standard deviation of the QTc dispersion for each electrocardiogram gave the same overall finding suggests that methodological problems are unlikely to account for our findings.

There is a recent deluge of positive data about the biological relevance of QTc dispersion. Ischaemia would seem to be one important determinant of QTc dispersion.[8,9] Moreno *et al* have also shown that QTc dispersion can be used after thrombolysis to tell whether or not it has successfully opened the culprit artery.[10] After coronary angioplasty successful revascularisation reduces QTc dispersion.[11]

CAUSES OF QTc DISPERSION

Why therefore should QTc dispersion be such a strong risk factor for cardiac death that in this study a highly significant effect can be shown in a relatively small number of patients?

Firstly, QTc dispersion could be due to patchy myocardial fibrosis, which leads to electrical inhomogeneity and anisotropic re-entry arrhythmias.[12-14] Indeed, Pye *et al* found that patients with sustained ventricular arrhythmias had increased QT dispersion,[15] although this is controversial.[16] Furthermore, QTc dispersion and fibrosis might be the end result of the three most adverse events in the heart—that is, ischaemia, left ventricular dilatation, and neurohormonal activation. For example, ischaemia contributes to QTc dispersion and it could be that QTc dispersion reflects fibrosis due not only to current ischaemia but also to all past major ischaemic insults and infarctions.

Secondly, QTc dispersion is also linked to left ventricular dilatation.[15] Indeed, our patients with peripheral vascular disease did have somewhat reduced left ventricular ejection fractions, which make it likely that some left ventricular dilatation had occurred. It is also well known that left ventricular dilatation confers a poor prognosis.[17]

Thirdly, patchy fibrosis could be a direct result of an activated renin-angiotensin system as both angiotensin

Key messages

- QTc dispersion is an easily obtained, non-invasive and cheap way of stratifying risk in patients with peripheral vascular disease
- A QTc dispersion of 60 ms had a 92% sensitivity and an 81% specificity of predicting cardiac death over the next five years in patients with peripheral vascular disease
- QTc dispersion was most prominent in those with diffuse coronary disease
- Measurements of QTc dispersion should help in deciding whether cardiac investigations and treatments should be undertaken in individual patients as well as helping to plan the most appropriate treatment for their peripheral vascular disease

II and aldosterone are thought to promote synthesis of myocardial collagen.[18]

CORONARY ANGIOGRAPHY, QTc DISPERSION, AND DEATH

Our study was too small to be categorical about the relation between QTc dispersion and coronary angiographic findings. Nevertheless, we did find that diffuse coronary disease was associated on average with a distinct increase in QTc dispersion even above that seen in triple vessel disease. In fact, the death rate was similar in those with triple vessel disease and those with diffuse coronary artery disease, even though QTc dispersion was greater in those with coronary artery disease. This suggests that QTc dispersion may be better at identifying the mechanism of death in patients with diffuse disease than in those with triple vessel disease. It is also worth pointing out that four out of six of our patients with diffuse coronary disease had diabetes mellitus, suggesting that QTc dispersion might be of particular value in diabetic patients.

In conclusion, we have found that QTc dispersion on a 12 lead electrocardiogram is a strong predictor of cardiac death in patients with peripheral vascular disease. Coronary angiographic findings suggest that diffuse coronary artery disease may be one of the main causes of prolonged QTc dispersion. Clearly these data require to be confirmed by further studies, but the causes of and the treatment for QTc dispersion now also deserve intensive investigation.

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Commentary: QTc dispersion may reflect vulnerability to ventricular fibrillation

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Peripheral vascular disease is a marker of coronary artery disease, and QT dispersion (the difference between the longest and the shortest measurable interval on the 12 lead electrocardiogram) is emerging as an important marker of serious arrhythmias and sudden death. To link these two markers is not at first intuitive, but the common ground lies in the spectre of coronary artery disease. Darbar *et al* correlate peripheral vascular disease not just with any coronary artery disease but with the type that carries the highest risk of death. With a modest patient cohort (49) cardiac death was strongly correlated with the QTc dispersion. Values of >60 ms had a 92% sensitivity and an 81% specificity in predicting this outcome. These are impressive results, particularly from a cheap, widely available test that is already performed in most such patients.

The history of QT dispersion is comparatively short, but it is emerging as a remarkably powerful predictor of cardiac death in such diverse areas as the long QT syndromes, heart failure, and hypertrophic cardiomyopathy. Its cellular basis is still not fully established, but QT variations in surface electrocardiography in humans have been correlated with epicardial monophasic action potential durations. Thus, for whatever reason and by whatever physics, regional variation and repolarisation can be revealed by conventional body surface electrocardiography. In the positive correlations of QT dispersion and mortality shown in previous studies it is easy to imagine a mechanism related through ventricular fibrillation. Dispersion of repolarisation, which may be reflected by QT dispersion, is crucial for the initiation and maintenance of ventricular fibrillation. Acute myocardial infarction that complicates primary ventricular fibrillation may even be predicted by QT

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