Acute psychological stress and the propensity to ventricular arrhythmias

Evidence for a linking mechanism

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Aims This study was designed to test the hypothesis that acute psychological stress is capable of inducing an increase in the dispersion of repolarization in patients with underlying coronary artery disease.

Methods and Results Twenty four patients undergoing elective coronary angiography were studied, 17 with significant coronary artery disease and seven with normal coronary arteries. Following coronary angiography they were subjected to a series of timed cognitive tests, well known to induce acute psychological stress. An individual’s perception of stress was assessed by visual analogue scales. Serial ECGs were recorded during the cognitive tests and QT, QRS and JT intervals measured from which QT, QRS and JT dispersion were calculated. Psychological stress was reported by the seven patients with normal coronaries and 14 of the 17 with coronary artery disease. In patients who experienced stress a marked increase in QT dispersion, reflecting JT dispersion, was observed in those with coronary artery disease (F=22.4, P=0.0001) but not in those without. At baseline there was no difference in QT dispersion between those with and without coronary artery disease (27–57 ms, 17–53 ms, P<0.5).

Conclusion Acute psychological stress induces an increase in QT dispersion in patients with underlying coronary artery disease due to changes in JT dispersion (rather than QRS dispersion). This suggests that psychological stress modifies the dispersion of repolarization through ischaemia related changes in action potential duration.

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See page 955 for the Editorial comment on this article
interval between all 12 leads of a standard ECG\textsuperscript{10}. In order to explore the arrhythmic link between acute psychological stress and coronary artery disease, we prospectively examined the ability of acute psychological stress to induce an increase in the dispersion of repolarization measured as QT dispersion, in patients with and without proven coronary artery disease.

**Methods**

Subjects were recruited from patients undergoing routine coronary angiography for known or suspected ischaemic heart disease. The study was subject to approval by the local ethics committee.

Patients defined as having coronary artery disease were those shown to have one or more stenoses of 70% or greater at angiography (the coronary artery group) whereas those in the normal coronary artery group had no stenoses and no evidence of myocardial infarction either clinically, electrocardiographically or angiographically. Usual medication was continued in all patients eligible for the study.

The exclusion criteria were: an absence of sinus rhythm, significant valvular disease, severe coronary artery disease (e.g. left main stem disease), the presence of right or left bundle branch block, the presence of antiarrhythmic medication other than beta-adrenergic blockers, requirement of an anxiolytic prior, during or post angiogram, or a poor command of the English language. Due to its class III activity, any patient on sotalol was not studied.

After the angiogram when the patient was settled on the ward, he or she undertook a series of five different cognitive tests involving: timed serial subtraction, a word fluency task, reverse sequential memory tasks and an impromptu speech without hesitation. Each task lasted 2 min and verbal instructions emphasized the need for speed and accuracy. The ability of these tests to induce psychological stress has been extensively validated in previous research\textsuperscript{11}. A range of tasks were used because of the known inter-patient variability to different test types in order to optimize the likelihood of any particular patient being psychologically stressed. For consistency the initiator of the tasks was the same investigator in all cases, having had no contact with the patients prior to the study. There were three observers.

Twelve lead ECGs were recorded using a system which simultaneously acquires the individual leads (Marquette MAC VU). ECGs were recorded at baseline (prior to the tests), within the first 30 s of each new test and at the end of each 2 min period.

An index of the subjective stress experienced was obtained using visual analogue scales. An individual was considered to report subjective stress where an increase from baseline on the sum of the four analogue scales was observed.

**ECG analysis**

All ECGs were recorded at 50 mm . s\textsuperscript{−1} and measured as previously described by a single unblinded observer\textsuperscript{9}. A random sample of ECGs was analysed by a second observer who was completely blind to coronary status. The QRS complex was defined as the distance from the onset of the Q wave to the end of the S wave and the JT interval, as the distance from the J point to end of the T wave. Leads where the end of the T wave could not be accurately identified were excluded from analysis, as were ECGs with less than seven leads suitable for measurement\textsuperscript{12}. QT, QRS and JT intervals were measured in three consecutive complexes and the average value calculated. QT, QRS and JT dispersion were then calculated as the greatest inter lead difference between the QT, QRS and JT intervals, respectively. No correction was made for heart rate since QT dispersion, unlike the QT interval, has not been shown to be dependant on heart rate\textsuperscript{13}. QRS and JT dispersion were analysed by means of two way repeated measures analysis of variance (ANOVA).

**Results**

Twenty four patients were studied: seven with normal coronary arteries and 17 with coronary artery stenoses. Five patients in the coronary artery disease group had had a previous myocardial infarction: three treated with thrombolysis, resulting in well preserved left ventricular function (ejection fractions: 0·7, 0·73, 0·59) and two patients had evidence of myocardial infarction on the basis of ECG and echocardiography findings, although there was no specific history (ejection fractions: 0·52 and 0·49). The remaining 12 patients in the coronary artery disease group had no prior history or ECG evidence of myocardial infarction: all had normal left ventricular function with the exception of one patient with an ejection fraction of 0·53 and global hypokinesis. The average ejection fraction in the coronary artery disease group was 0·71. The average ejection fraction in the normal group was 0·8. The 70% stenosis was a minimum criterion for inclusion in the study, but of those included in the CAD group, 71% had multi-vessel disease and 88% were referred for re-vascularization.

The cognitive tests produced subjective stress in 14 patients with coronary artery disease and all seven without coronary artery disease. In response to this psychological stress there was an acute increase in QT dispersion (Fig. 1) in those with underlying coronary artery disease, but not in those with normal coronaries. The increase in QT dispersion reflected an increase in JT dispersion (representing the dispersion of action potential duration) (F=22·4, df=1·19, P<0·00001) whereas the QRS dispersion (used as a measure of conduction) was not influenced by psychological stress in any patient (F=3·63, df=1·19 ns) (Fig. 2). In contrast, those patients with coronary artery disease who experienced no stress showed no increase in QT dispersion.

Only one patient in the coronary artery disease group experienced angina during mental stress testing. ST depression occurred in this individual and in one other patient in the coronary artery disease group who did not experience angina. A further patient developed T wave
changes without angina. All these three patients responded to psychological stress with an increase in QT dispersion, but in this respect their behaviour was no different from the other patients with coronary artery disease who increased their QT dispersion without developing ST or T wave changes or any angina during the tests. No one in the normal group experienced angina or developed ST changes. Psychological stress producing an increase in QT dispersion was observed both in the patients taking beta-adrenergic blockers and in those not using these drugs. There was no significant relationship between peak heart rate and peak QT dispersion \((P \geq 0.4)\), change in heart rate and change in QT dispersion \((P \geq 0.3)\) or peak heart rate and peak stress \((P \geq 0.3)\).

QT intervals were measurable in an average of 9-5 leads and there was no significant difference in resting QT dispersion in patients with \((27–57\,\text{ms})\) and without coronary artery disease \((17–53\,\text{ms})\) \((P \geq 0.5)\) and the values obtained were all within the range of accepted normality. Mean inter-observer difference in QT dispersion was 10.

**Discussion**

This study provides evidence of an electrophysiological mechanism to link acute psychological stress with the propensity to ventricular arrhythmias in patients with coronary artery disease. We have prospectively demonstrated that induced psychological stress results in an increase in the inhomogeneity of myocardial repolarization (assessed as QT dispersion) in patients with underlying coronary artery disease but not in those with normal coronaries.

Hitherto, indirect and circumstantial evidence has strongly suggested that psychological stress may be an important factor in the development of malignant arrhythmias. Although acute psychological stress is a recognised trigger of myocardial ischaemia in patients with coronary artery disease\(^\text{[14]}\) and disasters such as the 1994 New York earthquake have been associated with a fivefold increase in sudden death in patients with coronary artery disease\(^\text{[15]}\) and documented arrhythmias\(^\text{[16]}\), interpreting such observations has to date been largely speculative. Similarly, recognition that everyday stressors such as driving and public speaking produce ST depression, ventricular ectopy and runs of ventricular tachycardia\(^\text{[17,18]}\) has not provided the causal link between psychological stress and its propensity to precipitate lethal arrhythmias in patients with ischaemic heart disease. Problems encountered in trying to systematically explore this area include the unpredictability of death, the retrospective nature of much of the data, an absence of basic electrophysiological human data and the very heterogeneity of stress in people.

To date the strongest evidence for the arrhythmogenic potential of acute psychological stress has come from animal experiments\(^\text{[19–21]}\). Extensive experimental electrophysiology has shown an increase in the dispersion of repolarization between differing areas of the ventricle to be central to the genesis of arrhythmias induced by acute myocardial ischaemia\(^\text{[22]}\). Over recent years there has been increasing interest in the use of the standard 12-lead ECG, from which the QT intervals in individual leads can be measured to provide a non-invasive index of the dispersion of repolarization, known as QT dispersion\(^\text{[19]}\). Using this technique, we have previously explored the potential to produce acute or dynamic increases in QT dispersion in response to acute ischaemia in patients with coronary artery disease\(^\text{[9]}\). In the present study we have prospectively shown that patients with coronary artery disease in whom psychological stress is induced also produced marked increases in QT dispersion. It is of note that the small numbers of patients with coronary artery disease who did not experience stress in response to the cognitive tests produced no such increase in QT dispersion. Similarly, there was no increase in QT dispersion in the control group who experienced stress but who had normal coronary arteries. This suggests that ischaemia is a critical component of the response to psychological stress.

This study was not designed to explore the relationship between ischaemia and psychological stress in detail. Of note, only three patients developed clinical signs of ischaemia (one angina and ST depression, one ST depression alone and one T wave changes). It seems likely, however, that the observed increases in the
dispersion of repolarization (assessed as QT dispersion) was also a function of ischaemia, even in the patients who failed to produce clinical evidence of ischaemia. Deanfield and colleagues have previously documented the propensity of mental arithmetic to induce widespread defects in myocardial perfusion (assessed by positron emission tomography) in patients with coronary artery disease. Of interest, 50% of their patients developed perfusion defects in response to stress without either developing angina or ST depression [23]. Similarly Rozanski et al. reported that 72% of 39 patients with confirmed or probable coronary artery disease developed wall motion abnormalities (assessed by nuclear ventriculography) in response to a range of mental stress tests but only angina or ST changes in the minority (17% and 23% respectively) [24]. Thus a consistent theme from these studies and our own work is that the ST and T wave changes may not reflect degrees of underlying ischaemia which are nonetheless of electrophysiological importance. Our findings may have some bearing on the recurrent paradox that monitored patients dying from arrhythmias, thought to be on an ischaemic basis, rarely demonstrate ST changes prior to the arrhythmia.

During early ischaemia, changes occur to the action potential duration rather than to conduction time, but when the dispersion of repolarization is assessed simply as QT dispersion it is not possible to distinguish between these different influences. For this reason we sought to distinguish these influences by separately measuring JT and QRS dispersion. This provides an approximation of the dispersion of inter-ventricular conduction time (from the QRS segment) and of dispersion of activation to repolarization (from the JT segment). Acute psychological stress in patients with underlying coronary artery disease produces acute increases in QT dispersion which are almost entirely due to dispersion in action potential duration (JT dispersion) with dispersion in inter-ventricular conduction time (QRS dispersion) remaining relatively constant. The exact mechanisms underlying these effects on action potential duration remain unclear but since the action potential duration rather than conduction time was affected and the changes only occurred in those with underlying coronary artery disease who experienced mental stress, it is likely that the increased dispersion of repolarization resulted from inhomogeneous ischaemia mediated through the sympathetic nervous system.

Human studies of early ischaemia suggest action potential shortening is of the order of 10–20% [25] but in the presence of prolonged or severe ischaemia, this shortening can be considerably more pronounced before inexcitability develops. Adrenergic stimulation has the potential to produce inhomogeneous influences on action potential duration [5,26]. Lengthening or shortening of action potential duration, in any given area, is determined by the predominance of alpha or beta adrenoreceptor influences and either effect may be further modified by co-existent ischaemia [27] (see Fig. 3).

Figure 2 The changes in QRS (■) and JT (□) dispersion in response to acute psychological stress: QRS dispersion (representing changes in the dispersion of conduction) shows no significant change with psychological stress whereas JT dispersion (reflecting the dispersion of action potential duration) increases in response to psychological stress in patients with coronary artery disease but not in those with normal coronaries. Data are shown with 95% confidence intervals.

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<th>Patients with normal coronary arteries</th>
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These influences are likely to be disparate in different areas of the myocardium particularly if there is regional ischaemia or previous infarction.

One of the underlying issues is whether or not beta blockade will ameliorate these changes. The present study was not designed to address this issue but certainly psychological stress producing an increase in QT dispersion was observed in both the patients taking beta-adrenergic blockers and in those not using these drugs.

The relationship between psychological stress, myocardial ischaemia and autonomic modulation is complex and requires further elucidation. Not only may these interactions be inhomogeneous within an individual but may differ quite markedly between individuals with coronary artery disease, as suggested by the work of Bairey et al. They again convincingly demonstrate that psychological stress induces regional wall motion abnormalities in patients with coronary artery disease, but report a discordant effect of beta-blockade on this response, which would be consistent with a variable role of the autonomic nervous system.

This study is the first to demonstrate a plausible pro-arrhythmic mechanism to link psychological stress with the propensity to malignant arrhythmias in individuals with coronary artery disease. We have demonstrated that acute psychological stress induces increases in the dispersion of repolarization, as assessed by QT dispersion, in patients with coronary artery disease and we suggest that the mechanism underlying these electrophysiological changes is one of ischaemia.

This study was not designed to induce arrhythmias, rather to explore the propensity for stress to induce increases in QT dispersion. In the real world, where much greater mental stress may be encountered, we suggest that the stressors which precede actual arrhythmias might induce more profound increases in QT dispersion.

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References


