Pathophysiology and time course of silent myocardial ischaemia during mental stress: clinical, anatomical, and physiological correlates

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Abstract

Objective—To define the prevalence and pathophysiology of myocardial ischaemia induced by mental stress in patients with coronary artery disease and exercise inducible ischaemia, and to determine the correlation between the severity of coronary artery disease and ischaemia induced by speech.

Design—Prospective cohort study.

Setting—Tertiary care academic institution.

Patients and protocol—47 patients with coronary artery disease and 20 normal controls were studied using standardised exercise and mental stress. The ambulatory nuclear vest provided continuous measures of left ventricular ejection fraction and relative volume changes: an ischaemic response to mental stress was defined as a decrease in ejection fraction of ≥ 5% for ≥ 60 s. Severity of coronary artery disease was assessed by the extent of thallium reversibility on exercise testing and the severity of angiographic disease.

Results—23 (49%) of 47 patients with coronary artery disease had an ischaemic response to mental stress which occurred early, and was sustained throughout the task and associated with an increase in end systolic volume. In contrast, the pattern of left ventricular response in the remaining 24 patients (51%) resembled that in the normal controls. Patients with mental stress induced ischaemia tended to have greater severity of coronary disease (mean (SD) total number of diseased vessels 1.9 (0.8) v 1.4 (0.9), P = 0.07), more frequent exercise induced angina (17/23 v 7/24, P = 0.003) and lower increases in heart rate (36 (11) v 49 (23) beats per min, P = 0.023) and systolic blood pressure (32 (19) v 45 (18) mm Hg, P = 0.03) during exercise. Left ventricular responses to speech and exercise were compared in the 23 patients with mental stress induced ischaemia: mental stress was associated with a greater decrease in ejection fraction at comparable increases in rate pressure product (6.5 (6.3)% v 4.7 (11.2)%, P = 0.0001).

Conclusions—These findings suggest that mental stress induction of myocardial ischaemia is common in patients with stable coronary artery disease. Susceptible patients may have more functionally severe coronary disease.

The time course, pattern, and haemodynamic features of mental stress induced ischaemia suggest a dynamic decrease in coronary supply.

Keywords: mental stress; myocardial ischaemia; coronary artery disease; left ventricular function

Several studies have shown that laboratory modelled mental stress is an effective trigger of myocardial ischaemia in patients with coronary artery disease. The prevalence of ischaemic responses varies with the sensitivity of the assessment technique from about 20% using ST segment depression to 70% with positron emission tomography of myocardial hypoperfusion. It is now appreciated that ST depression may be a late and relatively insensitive indicator of myocardial ischaemia. There is compelling evidence that mental stress provokes myocardial ischaemia, with concordance of perfusion defects and wall motion abnormality during mental stress and exercise. Mental stress induced ischaemia resembles daily life ischaemia in that both are usually asymptomatic and occur at a lower heart rate and blood pressure than exercise induced ischaemia. Despite this evidence of the effectiveness and distinctive mechanism of mental stress induced ischaemia important questions remain:

(a) What is the prevalence of mental stress induced ischaemia in patients with coronary artery disease and exercise inducible ischaemia?

(b) Is there a correlation between the extent of coronary artery disease and the inducibility of ischaemia by mental stress?

(c) Is there a distinctive time course and pattern of left ventricular dysfunction which may elucidate the underlying pathophysiology of mental stress induced ischaemia?

We addressed these questions by utilising a novel nuclear technology, the nuclear vest, to provide continuous accurate assessment of relative left ventricular volume during exercise and mental stress. Our primary objective was to define the prevalence, and delineate the time course and pathophysiology of mental stress induced ischaemia. A second objective was to determine whether conventional indices of the severity of coronary artery disease predict vulnerability to mental stress induced ischaemia.
Pathophysiology of silent studied normal patients thallium with patients less branch disease based on symptoms and reversible thallium defects on recent, clinically indicated thallium scintigraphy during Bruce protocol exercise. Patients with coronary artery disease were excluded if they had bundle branch block, unstable angina in the previous 3 months, myocardial infarction in the previous 6 months, or previous coronary bypass surgery.

THALLIUM SCINTGRAPHY WITH EXERCISE AND CORONARY ANGIOGRAPHY
Thallium scintigraphy data were available in 45 of 47 patients for interpretation by two experienced observers blinded to clinical and angiographic data. Scintigraphy was performed after injection of 2 mCi of thallium-201 during maximum symptom limited exercise by Bruce protocol, with planar images obtained at 5 mins and 4 h after exercise. The anterior, 45°, and 70° left anterior oblique planar images were acquired for 10 min each and interpreted according to visual scores as previously described by one of us (MRF). In summary, each planar image was analysed in three segments per view and scored as: 0, normal; 1, mild; 2, moderate; or 3, severe reduction. A thallium ischaemic score was calculated as the total postexercise score minus the total 4 h redistribution score. The results of coronary angiography in 40 of 47 patients with coronary artery disease performed for clinical indications within the previous 12 months were interpreted by an experienced angiographer independent from the study. The number of vessels with ≥ 50% stenosis was determined and a jeopardy score as determined by Califf et al, with maximum score of 9, was derived.

EXPERIMENTAL PROTOCOL
Informed consent was obtained from all participants. The protocol was approved by the institutional ethics committee on 23 October 1990. Basic demographic data, cardiac symptoms ratings, and medication status were verified. When possible, antianginal medication was withheld for 48 h before the study. Table 1 gives the proportion of patients who received antianginal medication during testing. All participants refrained from food, caffeine, and nicotine for 2 h before the start of testing.

Studies were completed on a single day between 9 am and 1 pm. The nuclear VEST was applied, a pre-exercise control obtained, and participants exercised using the protocol of the National Institutes of Health (NIH). After a 15 min recovery period they were seated in a sound deadened chamber where a series of four mental stress tasks, including three computer-simulated arousal tasks and a personally relevant speech, was applied. Each task was preceded by a 10 min control period for stabilisation of haemodynamic parameters; pre-exercise control was standing, whereas premental stress control was sitting. The protocol lasted approximately 4 h, with exercise first and speech last. Because of the higher frequency of abnormal responses during speech, this report is limited to comparisons of exercise and speech responses.

Physiological indices measured during control and stress periods included continuous recording of heart rate, frequent measures of blood pressure using an automated cuff, and VEST derived measures of left ventricular ejection fraction, with relative end systolic and end diastolic volumes. An event marker on the VEST was used to permit precise temporal alignment of VEST derived measures with each time point in the task. Participants were questioned about anginal symptoms at the conclusion of each task.

VEST application
Each participant was injected with red blood cells labelled in vitro with 25 mCi of technetium-99m. Electrocardiographic electrodes recorded an inferior and a modified V5 lead. A multiple gated equilibrium scintigraphic study of the cardiac blood pool was obtained in the 45° left anterior oblique view and left ventricular ejection fraction was calculated using standard multiple regions of interest and background subtraction as previously described. The radionuclide detector was positioned over the left ventricle using a gammacamera to determine optimal placement; this was verified by static gammacamera images at the beginning and end of each study. The detector was secured by a plastic garment around the chest wall.

Radionuclide data from the VEST were analysed using a dedicated microcomputer. Cardiac cycles were rejected if the RR interval varied more than 20% of the average of the previous four cardiac cycles. Ejection fraction was calculated from stroke counts (end diastolic minus end systolic counts divided by fixed background corrected end diastolic counts). The background was determined by the computer to give a baseline ejection fraction similar to that determined with the gated equilibrium study. The electrocardiographic gated radionuclide activity data were summed in 30 s intervals and trend plots generated. We determined heart rate, ejection fraction, relative end systolic and end diastolic volumes expressed as a per cent of end diastolic volume at the start of the study. The accuracy and reproducibility of ejection fraction measurement have been validated by ourselves and Yang et al.

Exercise testing
Participants underwent an upright treadmill exercise test using the protocol of the NIH with 12 lead electrocardiography. It was chosen because the more gradual increase in heart rate and systolic blood pressure provided an opportunity to match heart rate and blood pressure increases during mental stress.
Exercise end points were moderate chest pain, ST depression >2 mm, ventricular arrhythmia, fatigue, or attainment of a target heart rate.

**Mental stress testing**
Without forewarning, participants were instructed to speak for 3–5 min on their personal faults or undesirable habits to an assembled audience of stern, white coated attendants. Standard instructions were given, as described by Rozanski et al. Participants were given 4 min to compose their speech, during which they were alone in the experimental chamber. The audience entered the chamber and the participant started to speak. Haemodynamic measurements were made during the preparation and delivery phases of speech.

**DEFINITION OF ISCHAEMIC RESPONSES DURING EXERCISE AND MENTAL STRESS**
An ischaemic response to exercise was defined as an increase of ≤ 5% in left ventricular ejection fraction at peak exercise. An ischaemic response to mental stress was predefined as a decrease of ≥ 5% lasting ≥ 60 s in left ventricular ejection fraction.

**DATA PROCESSING AND ANALYSIS**
Baseline values for heart rate, systolic and diastolic blood pressures, left ventricular ejection fraction, and relative end systolic and end diastolic volumes were determined for exercise and mental stress by taking the mean of these measures during the control period preceding each task. Change scores in these physiological indices were derived by subtracting the appropriate control value from the task value: hence change values corrected for differences in control values between tasks and between participants. Change scores were available at 30 s intervals during exercise and mental stress for VEST derived measures. Change values were available at 150 s intervals during exercise and 90 s intervals during mental stress for blood pressure. Data are presented as means (SD) unless otherwise noted.

The SAS statistical package (SAS Institute, Cary, NC, USA) was used for data analysis. Statistical significance was defined as P < 0.05. Dichotomous variables were compared using \( \chi^2 \) or Fisher's exact test. Continuous variables were compared using the unpaired \( t \) test for between participant comparisons and the paired \( t \) test for comparisons within participants. Repeated measures analysis of variance (ANOVA) was used to evaluate changes in physiological variables during tasks—that is, exercise and mental stress. A two way repeated measures ANOVA was used for comparison of the time course of change in physiological variables between groups, for example participants with and without speech induced ischaemia. An effect was considered significant only if the overall model had a value of \( P < 0.05 \). Multivariate logistic regression modelling of the number of cardiac risk factors, thallium reversibility score, use of \( \beta \) blockers, exercise induced angina, heart rate, and blood pressure responses to exercise was performed using the CATMOD procedure in SAS to predict the occurrence of mental stress induced ischaemia.

**Results**

**BASELINE CHARACTERISTICS**
All normal participants had a mean (SD) age of 42.2 (7.8) years and a mean of 1.4 (0.5) cardiac risk factors. Baseline left ventricular ejection fraction was 58 (10)%. Participants exercised for a mean of 17.7 (2.7) min during the NIH protocol, attaining mean increases in heart rate of 73 (14) beats per min, systolic blood pressure of 57 (15) mm Hg, diastolic blood pressure of 17 (8) mm Hg, and rate pressure product of 16797 (3301) beats per min x mm Hg. None had electrocardiographic evidence of ischaemia at peak exercise. Ejection fraction rose by 12 (10)%.

Table 1 gives baseline characteristics, including the thallium reversibility score on Bruce exercise testing, angiographic jeopardy score, and the total number of diseased coronary vessels in the 47 patients with coronary artery disease.

**BASELINE HAEMODYNAMIC VALUES BEFORE EXERCISE AND SPEECH**
Pre-exercise baseline data were obtained in the standing position, whereas premental stress baseline data were obtained in the sitting position. Repeated measures ANOVA within baseline periods showed no significant change in haemodynamic variables, indicating a stable physiological environment before task initiation. There were significant differences between pre-exercise and premental stress baseline values for heart rate (patients with coronary artery disease 73 (13) v 67 (12) beats per min, \( P = 0.0001 \); normal controls 78 (12) v 73 (9) beats per min, \( P = 0.001 \), left ventricular ejection fraction (patients with coronary artery disease 50 (8)% v 46 (8)%, \( P = 0.0001 \); normal controls 51 (8)% v 45 (8)%).

<table>
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<tr>
<th>Table 1 Baseline characteristics of 47 patients with coronary artery disease</th>
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<tr>
<td>Mean (SD) age (years)</td>
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<td>Mean (SD) years since diagnosis of coronary artery disease</td>
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<td>Mean (SD) total no of risk factors for coronary artery disease</td>
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<td>Family history of coronary artery disease (%)</td>
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<td>Acetylsalicylic acid (%)</td>
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<td>Mean (SD) total thallium reversibility score (Bruce exercise test)</td>
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<td>Mean (SD) jeopardy score</td>
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<td>Mean (SD) total no of diseased vessels (coronary stenosis &gt; 50%)</td>
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CCS, Canadian Cardiovascular Society.
groups based on the development of an ischaemic response during speech: 23 (49%) had an ischaemic response, whereas 24 (51%) had a non-ischaemic response. Mean (SD) peak changes in left ventricular ejection fraction were 8.0 (6.7%) in patients with mental stress induced ischaemia and 3.5 (6.8%) in those without an ischaemic response to speech (t = 5.8, P = 0.0001). The two groups had similar increases in heart rate and blood pressure; moreover, when changes in heart rate, and systolic and diastolic blood pressures during speech were correlated with the peak change in left ventricular ejection fraction there was no association in the sample of 47 patients or within the subgroup with mental stress induced ischaemia. Two patients with speech induced ischaemia and one without an ischaemic response to speech reported angina during speech; all had an ischaemic left ventricular response to the exercise protocol of the NIH.

Table 2 compares baseline demographic and cardiovascular disease characteristics of patients with and without an ischaemic response to speech. Patients with speech induced ischaemia seemed to have more severe coronary disease, as evidenced by trends for a greater number of cardiac risk factors, a higher thallium reversibility score, a higher angiographic jeopardy score, and a greater mean number of diseased coronary vessels. However, these differences were not statistically significant.

A greater proportion of patients without an ischaemic response to speech was taking β blockers (7/24 vs 2/23, P = 0.1). Furthermore, two way ANOVA for prediction of speech induced ischaemia showed a significant interaction between β blockers and angiographic evidence of disease severity. In the subgroup not taking β blockers (n = 38), patients with speech induced ischaemia had a significantly higher jeopardy score (4.7 (2.2) v 2.8 (1.7), P = 0.01) and a greater number of diseased vessels (2.1 (0.8) v 1.2 (0.8), P = 0.008) compared with those without an ischaemic response to speech. There were no significant differences in angiographic disease severity in the subgroup (n = 9) taking β blockers.

Table 3 gives responses to the exercise protocol of the NIH in patients with and without speech induced ischaemia. Patients with speech induced ischaemia more often terminated exercise because of angina, attained lesser increases in heart rate and systolic blood pressure at peak exercise, but had similar left ventricular responses to those of patients without an ischaemic response to speech. A multivariate model using previously described indices of the severity of coronary disease did not identify any index or combination of indices that were significant for predicting speech induced ischaemia.

Some 24 patients (51%) had an ischaemic response defined as an increase of ≤ 5% in left ventricular ejection fraction at peak exercise to the exercise protocol of the NIH, which did not correlate with speech induced ischaemia (table 4). In contrast to
speech induced ischaemia, exercise induced ischaemia was not associated with angiographic evidence of disease severity or thallium reversibility score (table 4).

PATHOPHYSIOLOGY OF SPEECH INDUCED ISCHAEMIA

Figure 1 shows the time course of change in rate pressure product, ejection fraction, and end systolic and end diastolic volumes during speech in 19 normal controls (one refused to participate). There was an initial small increase in rate pressure product during the preparation phase, which was accompanied by a rise in ejection fraction and end diastolic volume. Rate pressure product increased substantially at the onset of speech delivery and the ejection fraction was initially maintained. As speech delivery proceeded, the ejection fraction decreased to a value corresponding to that of baseline; this change seemed to be mediated through a mild rise in end systolic volume. The mean peak change in heart rate was 9-6 (11-9) beats per min, systolic blood pressure 20-2 (13-5) mm Hg, diastolic blood pressure 12-6 (8-1) mm Hg, left ventricular ejection fraction ~0-6 (1-6)%, end systolic volume 2-5 (0-9)%, and end diastolic volume 3-7 (1-4)%.

Figure 2 shows the time course of change in rate pressure product, ejection fraction, and end systolic and end diastolic volumes in patients with and without an ischaemic response to speech. Patients with speech induced ischaemia showed a significantly different pattern of ejection fraction response throughout the speech task compared with that of those without an ischaemic response; an initial decrease during preparation was followed by a more pronounced decrease during delivery (group effect P = 0.0001, time effect P = 0.0001). This was associated with a greater increase in end systolic volume, which was also accentuated at the start of speech delivery (group effect P = 0.0001, time effect P = 0.0001). End diastolic volume increased significantly more in the patients without an ischaemic response to speech, but the temporal pattern was not different (group effect P = 0.004, time effect P = 0.11). Differences between patients with and without an ischaemic response in ejection fraction, and end systolic and end diastolic volumes were already significant during the preparation phase of speech (P = 0.0002, P = 0.0007 and P = 0.03, respectively). The magnitude, pattern, and time course of heart rate, systolic and diastolic blood pressure, and rate pressure product increase during speech was identical in patients with and without an ischaemic response to speech. There were no differences in heart rate, blood pressure, or left ventricular responses with respect to β blocker mediation.

Left ventricular responses to speech and exercise in the 23 patients with mental stress induced ischaemia were compared at matched levels of rate pressure product to examine further the pathophysiology of mental stress induced ischaemia. Rate pressure product was comparable between stage 1 exercise and at the 2-5 min mark of speech delivery. At comparable rate pressure products, speech was associated with a substantial decrease in left ventricular ejection fraction compared with a mild increase with exercise (-6-5 (6-3)% v 4-7 (11-2)%, P = 0.0001 (fig 3)). Whereby, exercise was associated with a substantially greater increase in end diastolic volume (16-4 (9-2)% v 1-6 (5-5)%, P = 0.0001), speech was associated with a greater rise in end systolic volume (6-7 (6-3)% v 2-9 (11-3)%, P = 0.05) (fig 3).
Discussion

In this study, continuous assessment of left ventricular volume with the ambulatory nuclear VEST provided new insight into the pathophysiology of myocardial ischaemia during mental stress. Our data show that the ischaemic response to personally relevant speech was sudden, starting in the preparation phase and accentuated during speech delivery. The decrease in ejection fraction was associated with an increase in end systolic volume suggesting myocardial ischaemia. In contrast, patients with a non-ischaemic response resembled normal controls by showing maintenance of, or slight increase in, ejection fraction, with accompanying increase in end diastolic volume but no change in end systolic volume.

Provocation of ischaemia during mental stress was not attributable to a greater increase in myocardial oxygen demand in patients with speech induced ischaemia. Rather patients with and without an ischaemic response to speech had similar increases in heart rate and blood pressure; moreover, patients with speech induced ischaemia had lesser increases in end diastolic volume during speech than those without an ischaemic response to speech. These data suggest that patients with speech induced ischaemia had a relative reduction in myocardial oxygen supply during mental stress, which could be caused by either greater fixed coronary stenoses or greater dynamic reduction in coronary blood flow. Our data show that patients with speech induced ischaemia had more severe fixed coronary artery stenoses; this trend became significant when the confounding effect of $\beta$ blocker medication was removed.

Moreover, by performing a within subject comparison of physiological responses to mental stress and exercise in the 23 patients with speech induced ischaemia (fig 3), we have strong evidence that a dynamic reduction in coronary blood flow is important in the
development of ischaemia during mental stress—that is, at a matched level of myocardial oxygen demand, analogous to the two tasks, mental stress was associated with myocardial ischaemia (as evidenced by a decrease in ejection fraction), whereas the exercise response was non-ischaemic (as evidenced by an increase in ejection fraction). As this within subject comparison effectively matches conditions between exercise and mental stress for two of the three potential causes of ischaemia—that is, severity of fixed coronary disease and increase in myocardial oxygen demand, the only factor accounting for mental stress induced ischaemia is a dynamic reduction in coronary blood flow. In keeping with our data, Yeung et al.\textsuperscript{14} reported direct angiographic visualization of coronary vasoconstriction during mental stress, supporting the concept of reduced coronary flow as a significant pathophysiological mechanism of mental stress induced ischaemia. Furthermore, Yeung et al.\textsuperscript{14} found that mental stress induced coronary vasoconstriction occurred only at sites with atherosclerotic plaque; one could postulate that more extensive coronary disease would lead to more opportunity for vasoconstriction and therefore a greater likelihood of myocardial ischaemia during mental stress.

Of note, our matching of the level of increase in rate pressure product between tasks may not represent accurate estimates of myocardial oxygen demand in the two circumstances. As can be seen from fig 3, the increase in rate pressure product was determined by different factors in exercise versus speech. An additional determinant of myocardial oxygen demand not matched in this comparison is end systolic volume, with much greater increases in this index during speech. Consideration of the time course of left ventricular volume change during speech (fig 2), however, would suggest that the greater rise in end systolic volume accompanies rather than causes the decrease in ejection fraction during speech.

Although indices of disease severity tended to be greater in patients with mental stress induced ischaemia, a multivariate model did not predict mental stress induced ischaemia. This may reflect either low statistical power due to the limited sample size, or the difference in pathophysiology of ischaemia during exercise versus mental stress in patients with coronary artery disease.

Although the study was designed to test patients not taking antianginal medication, this was not always possible. A subsidiary analysis was planned to examine the potential protective effect of \(\beta\) blockers, in particular against mental stress induced ischaemia.\textsuperscript{25} We found that treatment with \(\beta\) blockers may have protected against mental stress induced ischaemia given the observed trends for more patients without an ischaemic response to speech to be taking \(\beta\) blockers and those with speech induced ischaemia who were not taking \(\beta\) blockers to have significantly greater angiographic evidence of disease severity. Such a protective effect may be mediated by an increase in coronary reserve during mental stress analogous to the observations by Bortone et al.\textsuperscript{16} on the effect of \(\beta\) blockers to increase coronary reserve during exercise testing in patients with coronary artery disease. Bairey et al.\textsuperscript{25} also provided data suggesting that \(\beta\) blockers may protect against mental stress induced ischaemia.

Prevalence of mental stress induced ischaemia in our patients with coronary artery disease and thallium reversibility during standard exercise testing was 48%. This value accords with that of previous studies which have used sensitive measures to assess myocardial ischaemia during mental stress.\textsuperscript{44} It is noteworthy that, despite all our patients having thallium reversibility on recent Bruce exercise testing, the sample had relatively mild coronary disease, as evidenced by their Canadian Cardiovascular Society functional class, infrequent ST depression during NIH exercise, and angiographic jeopardy score.

In this study, an ischaemic response to exercise (defined as either an ischaemic left ventricular ejection fraction response or ST depression \(>1\ mm\)) did not correlate with indices of severity of coronary artery disease. This lack of correlation is unexpected and may be the result of the fact that the patient sample had moderate disease severity.

In conclusion, these findings suggest that vulnerability to mental stress induced ischaemia is related to more extensive angiographic disease and that the mechanism of this association is through a dynamic reduction in coronary flow at the site of atherosclerotic plaques.

LIMITATIONS

Our study used a measure of global ventricular function—that is, left ventricular ejection fraction to assess ischaemia during mental stress. It could be argued that the ejection fraction decrease of 5% during mental stress may not represent ischaemia but may be secondary to changes in afterload. However, we showed that identical changes in heart rate and blood pressure were observed in patients with or without a decrease in ejection fraction during mental stress. In addition, the magnitude of heart rate and blood pressure change did not correlate with the magnitude of ejection fraction change in either the study sample or the subgroup who developed ischaemia during speech. Hence, it is unlikely that the reduction in ejection fraction is explained by changes in afterload.

There were differences in left ventricular ejection fraction and end diastolic volume between exercise and speech controls. The higher control value of ejection fraction before exercise is likely to be related to upright posture and anticipation of exercise. The lower end diastolic volume before speech is related to decay in counts, and gradual loss of the \(99\text{mTc}\) label to red blood cells over the time course of the protocol, as well as a reduction in blood volume after exercise. The use of change values to compare responses to
exercise and speech tasks corrected for these small differences in control values.

**IMPLICATIONS**

Our findings suggest that mental stress induced ischaemia is a common phenomenon in patients with coronary artery disease and exercise inducible ischaemia. Patients with a normal exercise response on ECG may have ischaemic responses to mental stress.

It is unknown whether vulnerability to mental stress induced ischaemia has prognostic significance or predicts silent ischaemia during daily life. Given the evidence that mental stress induced ischaemia is mediated mainly through coronary vasoconstriction, mental stress testing may provide data on the functional severity of coronary disease which is complementary to that of standard exercise testing.

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