Systematic review of mental stress-induced myocardial ischaemia

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Revised 5 August 2002; accepted 7 August 2002

KEYWORDS
Mental;
Stress;
Myocardial;
Ischaemia

Introduction

There is growing evidence that psychosocial stress can influence the natural history of coronary heart disease. Epidemiological studies indicate that psychosocial factors both contribute to the development of coronary artery disease (CAD), and increase risk of cardiac dysfunction and the likelihood of cardiac events in susceptible patients with established disease. An important method of assessing effects on cardiac function is by measuring transient ischaemic responses to standardized mental stress tests. Mental stress-induced myocardial ischaemia (MSIMI) is analogous to exercise stress ischaemia, except that the stimulus is psychological rather than physical. MSIMI has been studied with a number of different imaging techniques and with a range of stressful stimuli. But several investigations have involved small numbers of patients, and the medication status of patients has been variable. This has resulted in diverse findings concerning the prevalence of MSIMI, the conditions in which it is elicited, the type of patients who are most susceptible, the mechanisms underlying the phenomenon, and its clinical significance. In an effort to clarify these issues, we have conducted a systematic review of studies in which myocardial ischaemic responses have been measured in response to standardized mental stressors in the laboratory and clinic.

Methods

Relevant articles were identified from searches of PubMed (http://www.ncbi.nlm.nih.gov/PubMed) between 1980 and 2002. Only articles in English language peer-reviewed publications were examined. We included studies that examined the link between standardized mental stress tests and myocardial ischaemic responses. Studies involving patients with CAD and healthy volunteers or patients without CAD were included. To ensure comprehensive data location, further searches were made for authors published in this field and review articles were used as sources. The bibliographies of all papers retrieved were hand searched to ensure as many articles as possible were obtained. A number of studies in this field have resulted in multiple publications, addressing...
different aspects of MSIMI. We only included the primary publication in the main review, but scrutinized subsequent publications when addressing ancillary issues. A wide range of stimuli were regarded as mental stressors, including mental arithmetic, simulated public speaking tasks, problem solving tasks, cognitive tasks like the Stroop colour/word interference task, psychomotor challenges such as mirror tracing, and tasks involving the recall of negative emotion. We excluded responses to the cold pressor test (immersion of hand or foot in iced water) and hyperventilation tasks, since these elicit reflex physiological, responses that are not psychological in origin. Studies were categorized according to the method used for assessment of myocardial ischaemia.

**Incidence of mental stress-induced myocardial ischaemia**

Methods of assessing myocardial ischaemia vary in cost, ease of administration, exposure of patients to radiation, sensitivity and test–retest reliability. We separately reviewed investigations that assessed transient MSIMI using the electrocardiogram (ECG) alone, echocardiography, the radionuclide ventriculogram, stationary or ambulatory nuclear probes, positron emission tomography (PET), and quantitative coronary angiography. A number of general points emerge from this review, regardless of the stressors used or method of ischaemia assessment. Firstly, MSIMI is much more common among patients with CAD than other groups, although significant numbers of individuals without known CAD also show ischaemic responses according to some criteria. Secondly, MSIMI is largely a silent phenomenon, and anginal chest pain is rare. Thirdly, the majority of CAD patients who experience MSIMI also demonstrate exercise-induced ischaemia. The proportion of patients who test positive for mental stress but negative for exercise-induced ischaemia is relatively low. Fourthly, the rates of MSIMI are highly variable across studies, even with the same method of assessing ischaemia and with similar mental stress tests. Finally, most studies to date have been carried out with men, and the extent of effects on mental stress in women is not known.

**Studies involving ECG assessment**

Eight studies have used ST segment depression as the primary method for assessing myocardial ischaemia, although other investigators have included the ECG along with more sophisticated imaging techniques. Mental arithmetic has been the commonest mental stressor, but general knowledge quizzes, reaction time tasks, simulated speech tasks, and the Stroop test have also been employed. The incidence of MSIMI in patients with CAD averaged 30% using ECG criteria, with a range across studies of 12–55% (Table 1). The lowest incidence was observed in a study in which patients were medicated with beta-blockers and calcium antagonists, while in other studies patients were withdrawn from medication. A study of patients with vasospastic angina and no significant CAD showed an incidence of 28%. In a large cohort of the siblings of patients with premature CAD, none of the participants displayed MSIMI. Two other studies included individuals without CAD. No MSIMI was observed by Jennings and Follansbee in a non-CAD control group, while Specchia et al. reported that 18% of patients with chest pain but without significant stenosis on angiography fulfilled ECG criteria for MSIMI. It is possible that some of these individuals had vasospastic angina.

Interestingly, studies that have assessed ECG secondarily to cardiac imaging have reported rather lower rates of ST-segment depression than those shown in Table 1. For example, in the Physiological Investigations of Myocardial Ischemia (PIMI) study, 58% of cardiac patients displayed MSIMI as defined by worsening wall motion abnormalities and/or left ventricular ejection fraction reductions ≥8%, but the incidence of ECG-defined ischaemia was only 2–3%. Andrews et al. found that 53% of patients exhibited new wall motion abnormalities during mental stress, but only 7% showed ST-segment depression. The explanation for this discrepancy is not clear.

**Studies using radionuclide ventriculography**

Studies using radionuclide ventriculography are the most numerous in the literature. Radionuclide ventriculography is safe, non-invasive, widely available, and reproducible, and can be applied to both exercise and mental stress testing. The method can be used for serial imaging, and also has the benefit of identifying dysfunctions in arterial territories that can be related to abnormalities on catheterization or perfusion imaging.

Three criteria for MSIMI have been used (Table 2): the presence of new or worsening wall motion abnormalities, a fall in ejection fraction of ≥5%, and a fall in ejection fraction of ≥8%. The incidence of MSIMI using exclusively wall motion abnormality criteria averaged 46% in patients with CAD, while incidence on the ejection fraction
criteria selected by the investigators averaged 29%. However, in some studies ejection fraction criteria have proved more sensitive to mental stress.\textsuperscript{19} The large PIMI study reported an incidence of 58% using combined criteria.\textsuperscript{17} Aggregating across studies and using the most sensitive index in each case, we calculated an overall incidence of MSIMI of 48% in CAD patients, ranging from 34\textsuperscript{20} to 74\textsuperscript{10}. By contrast, across studies, 20.6% of volunteers or patients without known CAD displayed MSIMI. This is a sizeable proportion, but may be due in part to the use of the criterion of a decrease in ejection fraction of ≥5%. Becker et al.\textsuperscript{21} showed that 41% of a sample of healthy middle-aged men and women with low coronary risk factors showed MSIMI with the ≥5% criterion, but that only 10% displayed wall motion abnormalities, and 17% exhibited reductions of ejection fraction ≥8%. Consequently a fall in ejection fraction of ≥5% in response to mental stress may not be a sufficiently stringent criterion of myocardial ischaemia in the absence of wall motion abnormalities.

Radionuclide studies involving assessment of perfusion

The majority of radionuclide isotope studies have used radionuclide ventriculography to examine

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<th>Other results</th>
</tr>
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<tbody>
<tr>
<td>Schiffer et al.\textsuperscript{37}</td>
<td>36 Angina pectoris</td>
<td>Quiz</td>
<td>Off</td>
<td>ST segment depression criterion ≥1 mm</td>
<td></td>
</tr>
<tr>
<td>Specchia et al.\textsuperscript{51}</td>
<td>122 Chest pain</td>
<td>MA</td>
<td>Not stated</td>
<td>Same proportion (18%) of patients with and without significant stenosis on angiography show MSIMI</td>
<td></td>
</tr>
<tr>
<td>Jennings and Follansbee\textsuperscript{15}</td>
<td>11 CAD, 11 Controls</td>
<td>MA, RT, combined RT and MA</td>
<td>Off</td>
<td>ST segment depression criterion ≥1 mm</td>
<td></td>
</tr>
<tr>
<td>L’Abbate et al.\textsuperscript{36}</td>
<td>50 CAD</td>
<td>MA</td>
<td>Off</td>
<td>No MSIMI in controls</td>
<td></td>
</tr>
<tr>
<td>Specchia et al.\textsuperscript{16}</td>
<td>372 Angina pectoris</td>
<td>MA</td>
<td>Off</td>
<td>ST segment depression criterion ≥1 mm</td>
<td></td>
</tr>
<tr>
<td>Kral et al.\textsuperscript{14}</td>
<td>152 Siblings of patients with premature CAD</td>
<td>Stroop</td>
<td>Off</td>
<td>ST segment depression criterion ≥0.1 mm</td>
<td></td>
</tr>
<tr>
<td>Wong and Freedman\textsuperscript{12}</td>
<td>35 CAD mostly men</td>
<td>MA, Speech, Stroop, computer game</td>
<td>On</td>
<td>ST segment depression criterion ≥0.1 mV</td>
<td></td>
</tr>
<tr>
<td>Yoshida et al.\textsuperscript{13}</td>
<td>29 Vasospastic angina</td>
<td>MA</td>
<td>Off</td>
<td>ST segment depression criterion ≥0.1 mV</td>
<td></td>
</tr>
</tbody>
</table>

Mostly men: >75% male participants. MA=mental arithmetic; RT=reaction time task; Stroop=colour/word interference task.

The table above provides a summary of studies using ECG assessments of ischaemia.
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</thead>
<tbody>
<tr>
<td>Rozanski et al.⁷</td>
<td>39 CAD</td>
<td>MA, Speech</td>
<td>Off</td>
<td>59% Patients (WMA)</td>
<td>WMA developed in 74% with exercise</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LVEF criterion ≥% decrease</td>
</tr>
<tr>
<td>LaVeau et al.³²</td>
<td>12 Controls Mostly men 9 CAD 7 Controls All men</td>
<td>MA, Speech, Stroop</td>
<td>Some on Some off</td>
<td>36% Patients (LVEF) 8% Controls (WMA) Not stated</td>
<td>CAD: LVEF fell by 2% with MA, 1% with Stroop, and 3% with PS Controls: LVEF rose by 6% with MA, 13% with Stroop and 6% with PS</td>
</tr>
<tr>
<td>Bairey et al.¹⁰</td>
<td>19 CAD Mostly men</td>
<td>MA, Speech, Stroop</td>
<td></td>
<td>74% (placebo) 64% (metoprolol)</td>
<td>MSIMI defined as worsening wall motion abnormality</td>
</tr>
<tr>
<td>Ironson et al.³³</td>
<td>18 CAD 9 Controls All men</td>
<td>MA, Speech Anger recall</td>
<td>Off</td>
<td>44% Patients (WMA) 39% Patients (LVEF) 11% Controls (LVEF)</td>
<td>LVEF criterion ≥7% decrease</td>
</tr>
<tr>
<td>Miller et al.³⁸</td>
<td>33 CAD Men and women</td>
<td>Speech</td>
<td>Some on Some off</td>
<td>33% (WMA) 15% (LVEF)</td>
<td>LVEF criterion ≥5% decrease</td>
</tr>
<tr>
<td>Blumenthal et al.²⁰</td>
<td>132 CAD Mostly men</td>
<td>MA, MT, Speech, interview Speech</td>
<td>Some on, some off Off</td>
<td>34% (WMA)</td>
<td>49% Show WMA with exercise</td>
</tr>
<tr>
<td>Krittayaphong et al.⁵⁴</td>
<td>53 CAD Mostly men</td>
<td>Speech</td>
<td>Some on, some off Off</td>
<td>50% (WMA and/or LVEF) 21%</td>
<td>LVEF criterion ≥5% decrease</td>
</tr>
<tr>
<td>Jiang et al.⁶⁷</td>
<td>47 CAD Mostly men</td>
<td>Speech</td>
<td></td>
<td></td>
<td>MSIMI defined as new wall motion abnormality MSIMI less common in patients who were physically fit</td>
</tr>
<tr>
<td>Goldberg et al.¹⁷</td>
<td>196 CAD Mostly men</td>
<td>Speech, Stroop</td>
<td>Off</td>
<td>58%</td>
<td>LVEF criterion ≥5% decrease (17% with ≥8% decrease) Change in LVEF during mental stress inversely associated with change in systemic vascular resistance</td>
</tr>
<tr>
<td>Becker et al.²¹</td>
<td>29 Healthy volunteers Men and women</td>
<td>Speech, Stroop</td>
<td>None</td>
<td>10% (WMA) 41% (LVEF)</td>
<td>LVEF criterion ≥5% decrease (17% with ≥8% decrease) Change in LVEF during mental stress inversely associated with change in systemic vascular resistance</td>
</tr>
<tr>
<td>Jain et al.¹⁹</td>
<td>21 CAD 9 Controls Mostly men</td>
<td>MA, anger Recall</td>
<td>On</td>
<td>43% Patients (LVEF) 33% Patients (WMA) 33% Controls (LVEF)</td>
<td>LVEF criterion ≥5% decrease Change in LVEF during mental stress inversely associated with change in systemic vascular resistance</td>
</tr>
<tr>
<td>Andrews et al.¹⁸</td>
<td>18 CAD Mostly men</td>
<td>MA, Stroop, On interview</td>
<td></td>
<td>53% (WMA) 31% (LVEF)</td>
<td>LVEF criterion ≥5% decrease Pharmacological study: WMA prevented by nifedipine or atenolol</td>
</tr>
<tr>
<td>Hunziker et al.⁶⁸</td>
<td>10 CAD 11 Controls Men and women</td>
<td>MA</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Combined mental and physical stress leads to slightly greater decrease in LVEF, but similar haemodynamic response, to exercise alone</td>
</tr>
<tr>
<td>Bairey Merz et al.⁶¹</td>
<td>58 CAD 42 Controls Mostly men</td>
<td>MA, Speech Stroop</td>
<td>Off</td>
<td>64% Patients (WMA) 12% Patients (LVEF) 10% Controls (LVEF)</td>
<td>LVEF criterion ≥5% decrease</td>
</tr>
</tbody>
</table>

Mostly men: >75% male participants. MA=mental arithmetic; Stroop=colour/word interference task; LVEF=Left ventricular ejection fraction; WMA= wall motion abnormality.
alterations in left ventricular ejection fraction or changes in wall motion. Only three independent studies have used radionuclide perfusion imaging to correlate these criteria of myocardial ischaemia with the effects of mental stress on myocardial perfusion. In people without CAD, quantitative analysis has suggested that mental stress induces an increase in tracer uptake by the myocardium with no reversible perfusion defects.22

The three studies assessing myocardial perfusion with scintigraphy have all shown that high rates of new reversible perfusion abnormalities with mental stress (Table 3). Two Italian studies of post-infarction patients observed perfusion abnormalities in 70 and 89% cases, respectively.23,24 All the patients in a study by Kuroda et al.25 had reversible perfusion abnormalities. However, the participants in this study had relatively severe CAD, with a mean number of 2.2 diseased vessels in the study group. Only 50% of these patients had a fall in left ventricular ejection fraction ≥5%, suggesting that perfusion imaging is a more sensitive indicator of MSIMI than is a decrease in ejection fraction.

Studies using echocardiography

There are just a small number of echocardiographic studies in the literature, only two of which have involved more than 20 patients. The mean incidence of MSIMI across studies was 37% in patients with CAD, and 2% in controls (Table 4). However, the incidence of MSIMI between studies has ranged from 0 to 61%, despite the same stimulus (mental arithmetic) being used throughout. One study showed that the incidence of MSIMI was positively associated with the number of diseased arteries,6 while a second did not.9

Studies using the nuclear VEST

The VEST system provides a continuous beat-by-beat measure of left ventricular volumes and ejection fraction, using a radionuclide detector mounted in a vest-like garment. The technique has been validated against conventional blood pool imaging.26,27 Studies using the VEST system have all employed an ejection fraction decrease of ≥5% to indicate an abnormal cardiac response to mental stress, and consequently the same caveats exist as for radionuclide studies. The range of ischaemic responses varied across studies from 37 to 62% in patients with CAD, with an average of 41% (Table 5). In controls without known CAD, the incidence of MSIMI averaged 16%. One study with a sample selected for their predisposition to MSIMI showed highly reproducible ejection fraction responses over a 4–8 week period.28

Studies involving positron emission tomography (PET)

PET scanning is useful in assessing the effects of mental stress on the heart because it provides measures of coronary artery blood flow and myocardial perfusion. It has not generally been used to define MSIMI, but rather to assess mechanisms (Table 6). In volunteers without known CAD, resting blood flow is similar in the three arterial territories, and mental stress causes an increase in myocardial blood flow of some 30%.29 The increase in myocardial blood flow is correlated with

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<tbody>
<tr>
<td>Mazzuero et al.24</td>
<td>10 Post MI Mostly men</td>
<td>MA</td>
<td>Off</td>
<td>70% (scintigraphy) 67% (WMA)</td>
<td>Scintigraphy criterion: reversible segmental hypoperfusion</td>
</tr>
<tr>
<td>Bosimini et al.23</td>
<td>37 Post MI 22 Controls All men</td>
<td>MA</td>
<td>Off</td>
<td>89% (scintigraphy) 22% (ECG) 0% control</td>
<td>Scintigraphy criterion: reversible myocardial hypoperfusion ST segment depression criterion ≥0.1 mm</td>
</tr>
<tr>
<td>Kuroda et al.25</td>
<td>20 CAD Mostly men</td>
<td>MA</td>
<td>Off</td>
<td>100% (scintigraphy) 60% (WMA) 50% (LVEF) 30% (ECG)</td>
<td>LVEF criterion ≥5% decrease ST segment depression criterion not stated</td>
</tr>
</tbody>
</table>

Mostly men: >75% male participants. MA=mental arithmetic; Stroop=colour/word interference task; LVEF=Left ventricular ejection fraction; WMA=wall motion abnormality.
increases in catecholamine levels and rate-pressure product, and there is a decrease in coronary resistance. In contrast, Schoder et al.\textsuperscript{30} reported that in patients with CAD, there was a smaller rise in myocardial blood flow during mental stress, with no increase at all in regions with fixed perfusion defects. Similarly, a small study using the recall of real life anger-provoking episodes showed deficits of perfusion in diseased segments.\textsuperscript{31} There was no evidence of attenuation of myocardial blood flow during mental stress in this study, but all patients were taking cardiac medications. One quantitative result has been reported using PET scanning. Deanfield et al.\textsuperscript{5} showed that 75% of patients and no controls had MSIMI as defined by reversible abnormal regional myocardial perfusion. In this study, 38% of patients also fulfilled ECG criteria for MSIMI.

**Summary of trial data**

Summarizing across the 34 studies that provided quantitative information in this review, mental stress induces transient myocardial ischaemia in about 30% of CAD patients using electrocardiographic criteria, and 37–41% of patients with CAD with criteria based on decreased ejection fraction or wall motion abnormalities, while more than 75% of patients have perfusion abnormalities measurable by scintigraphy or PET scanning. Rates of MSIMI in patients without CAD or in healthy volunteers are in the range of 16% (VEST studies) to 21% (radionuclide ventriculography). These figures give only an approximate estimate of the incidence of transient MSIMI, since the studies differed markedly in size.

Differences in the sensitivity of the method of assessing myocardial function is responsible for some of the variation in rates of MSIMI. But the variability between studies using the same assessment technique is a result of other factors, including the following:

1. The selection of patients. The patients studied have varied substantially in the severity of CAD, cardiac history, age, and other selection criteria. Some studies have only include patients who had positive exercise stress tests,\textsuperscript{17} and this might have increased the likelihood of observing MSIMI.

2. Nature of stressors. Some mental stress tests are more potent than others in stimulating myocardial ischaemia. Radionuclide studies indicate that public speaking is more potent than mental arithmetic and the Stroop colour/word interference task in eliciting myocardial ischaemia in CAD.\textsuperscript{7,32,33} Blumenthal et al.\textsuperscript{20} found that a mirror tracing task was comparable with public speaking in terms of eliciting ischaemia, and that both were superior to mental arithmetic. A study specifically designed to assess reproducibility of responses over time showed that anger recall was a more consistent stimulus for MSIMI than mental arithmetic or

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</tr>
</thead>
<tbody>
<tr>
<td>Modena et al.\textsuperscript{6}</td>
<td>31 CAD 25 No CAD Mostly men</td>
<td>MA</td>
<td>Not stated</td>
<td>61% CAD 8% no CAD</td>
<td>Patients assessed during diagnostic coronary angiography MSIMI defined by wall motion abnormality Rate of MSIMI varies from 54% (one diseased vessel) to 83% (three diseased vessels)</td>
</tr>
<tr>
<td>Gottdien et al.\textsuperscript{9}</td>
<td>45 CAD 12 Controls All men</td>
<td>MA, Speech</td>
<td>Off</td>
<td>53% CAD 0% controls</td>
<td>MSIMI defined as new wall motion abnormality No relationship with number of diseased vessels</td>
</tr>
<tr>
<td>Soufer et al.\textsuperscript{50}</td>
<td>10 CAD 6 Controls All men</td>
<td>MA</td>
<td>Not stated</td>
<td>33% CAD 0% controls</td>
<td>MSIMI defined as new or worsening wall motion abnormality Study carried out in combination with cerebral PET scanning. Cortical activation associated with MSIMI</td>
</tr>
<tr>
<td>Okano et al.\textsuperscript{69}</td>
<td>7 CAD 8 No significant CAD Men and women</td>
<td>MA</td>
<td>Not stated</td>
<td>0%</td>
<td>MSIMI defined by wall motion abnormality or reduced LVEF</td>
</tr>
</tbody>
</table>

Mostly men: >75% male participants. MA=mental arithmetic; LVEF=Left ventricular ejection fraction.
the Stroop test. Reaction time tasks appear to be relatively ineffective inducers of myocardial ischaemia.

It should be noted that there are no standard agreed protocols for mental stress testing. It cannot be assumed that mental arithmetic, for example, is the same challenge in different studies. Few studies have collected subjective ratings, behavioural performance measures, or other indicators of stressfulness.

(3) Medication status. The use of cardiac medication has varied substantially across studies, and may have contributed to the range of results. Few direct comparisons have been reported. One double-blind study found that a limited effect of metoprolol reduced the incidence of MSIMI (denoted by worsening wall motion abnormality) from 74 to 64%. By contrast, Andrews et al. reported that wall motion abnormalities during mental stress were prevented by nifedipine or atenolol.

Mechanisms underlying mental stress-induced myocardial ischaemia

Haemodynamic responses and mental stress

The haemodynamic response to mental stress typically involves increased heart rate and blood pressure, the latter being sustained by raised systemic vascular resistance, cardiac output, or a combination of the two. Since myocardial ischaemia is triggered by elevated myocardial oxygen demand, and raised rate-pressure product, one possibility is that MSIMI is sustained by the same haemodynamic mechanisms that underlie exercise stress ischaemia.

Although there have been exceptions, the large majority of studies have demonstrated that myocardial ischaemic responses to mental stress occur at a lower rate-pressure product than exercise-induced ischaemic in the same individual patients. For example, Goldberg et al. reported that a speech task elicited myocardial ischaemia at an average rate-pressure product of 6800 (SD 3500), compared with 13 200 (SD 5400) for exercise. The CAD patients who displayed MSIMI in Rozanski et al.’s study had a mean rate-pressure product during mental stress of 11 297 (SD 1875), and 17 465 (SD 3484) during exercise. These findings clearly indicate that the mechanisms underlying MSIMI differ from those implicated in responses to exercise.

Results comparing the haemodynamic responses to mental stress of patients who do and do not exhibit MSIMI have been less consistent.

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<tbody>
<tr>
<td>Breisblatt et al.</td>
<td>35 Post MI Mostly men</td>
<td>MA, Stroop</td>
<td>Not stated</td>
<td>37%</td>
<td>LVEF criterion ≥5% decrease</td>
</tr>
<tr>
<td>Young et al.</td>
<td>12 Healthy volunteers All men</td>
<td>MA, Interview</td>
<td>Off</td>
<td>17%</td>
<td>LVEF criterion ≥5% decrease</td>
</tr>
<tr>
<td>Bairey et al.</td>
<td>18 Healthy volunteers Mostly men</td>
<td>MA, Speech, Stroop</td>
<td>Off</td>
<td>22%</td>
<td>LVEF criterion ≥5% decrease Similar blood pressure and heart rate responses in participants with and without MSIMI</td>
</tr>
<tr>
<td>Burg et al.</td>
<td>30 CAD Sex not stated</td>
<td>MA, Interview Reaction time</td>
<td>On</td>
<td>60% (interview) 50% (MA)</td>
<td>LVEF criterion ≥5% decrease Similar blood pressure and heart rate responses in participants with and without MSIMI. No LVEF decrease in response to reaction time task. No association between LVEF decrease and severity of CAD</td>
</tr>
<tr>
<td>Legault et al.</td>
<td>47 CAD All men Speech</td>
<td>Mostly off</td>
<td>49% (CAD) 0% (Control)</td>
<td>LVEF criterion ≥5% decrease</td>
<td></td>
</tr>
<tr>
<td>Vassiliadis et al.</td>
<td>8 CAD All men Video game</td>
<td>Off</td>
<td>62% (CAD) 25% (Control)</td>
<td>LVEF criterion ≥5% decrease</td>
<td></td>
</tr>
</tbody>
</table>

Mostly men: >75% male participants. MA=mental arithmetic; Stroop=colour/word interference task; LVEF=Left ventricular ejection fraction.
of studies involving radionuclide ventriculography have found that the cardiovascular responses to stress are greater in individuals who become ischaemic. Thus a secondary analysis of Rozanski et al. showed that patients who displayed severe wall motion abnormalities during speech and Stroop tasks showed greater systolic blood pressure and rate-pressure responses to tasks than did non-ischaemic patients. Similar results have been reported by others. By contrast, no associations between MSIMI and blood pressure or heart rate responses to stressors have been observed in studies using the nuclear VEST in patients with CAD or healthy volunteers.

One factor that may be relevant is the nature of the haemodynamic adjustment underlying the increase in blood pressure. Consistent associations between increased systemic vascular resistance and the development of ischaemia during mental stress tests have been identified. The observation that ejection fraction responses to mental stress are negatively correlated with systemic vascular resistance responses indicates that MSIMI might be due in part to an increase in afterload caused by peripheral vasoconstriction. By contrast, systemic vascular resistance is reduced with exercise. Jain et al. noted that systemic vascular resistance during mental stress increased in patients with CAD and decreased in healthy controls. It is interesting that in a study of healthy volunteers in which a substantial number showed left ventricular ejection fraction decreases of ≥5%, the changes in systemic vascular resistance were also negatively correlated with ejection fraction responses. Thus both in people with and without CAD, mental stress-induced ischaemia is associated with increases in systemic vascular resistance and afterload. These may be caused by a centrally-mediated neurogenic peripheral vasoconstriction.

A related factor is catecholamine release. Venous adrenaline and noradrenaline increase

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**Table 6: Studies using positron emission tomography**

<table>
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<tr>
<th>Author</th>
<th>Patients</th>
<th>Mental stressor</th>
<th>Medication (on/off)</th>
<th>Mental stress induced myocardial ischaemia (MSIMI)</th>
<th>Other results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deanfield et al.</td>
<td>16 CAD</td>
<td>MA</td>
<td>Not stated</td>
<td>75% (PET) 38% (ECG)</td>
<td>PET ischaemia defined as abnormal regional myocardial perfusion ST segment depression criterion ≥0.1 mm</td>
</tr>
<tr>
<td>Benight et al.</td>
<td>6 CAD</td>
<td>Anger recall</td>
<td>On</td>
<td>No evidence of decreased perfusion in CAD patients Greater perfusion in healthy coronary artery segments from controls than in diseased segments in CAD patients</td>
<td></td>
</tr>
<tr>
<td>Arrighi et al.</td>
<td>10 CAD</td>
<td>Not stated</td>
<td>On</td>
<td>Coronary flow reserve during mental stress lower in regions without significant epicardial stenosis than in those with significant stenosis Increase in myocardial blood flow blunted in regions without epicardial stenosis</td>
<td></td>
</tr>
<tr>
<td>Schoder et al.</td>
<td>17 CAD</td>
<td>MA</td>
<td>Off</td>
<td>Myocardial blood flow increases with mental stress in CAD and controls, but rise is greater in controls in regions with fixed perfusion defects, myocardial blood flow does not increase Coronary resistance similar in the two groups at rest, but fell in controls and was unchanged with mental stress in CAD</td>
<td></td>
</tr>
<tr>
<td>Schoder et al.</td>
<td>24 Controls</td>
<td>MA</td>
<td>Off</td>
<td>Increase in myocardial blood flow and decrease in coronary resistance with mental stress, correlated with increases in catecholamines and rate-pressure product</td>
<td></td>
</tr>
</tbody>
</table>

MA = mental arithmetic.
rapidly with mental stress, and in two studies were larger in men than women. The changes in plasma adrenaline were positively correlated with increases in heart rate, systolic blood pressure and rate-pressure product, and weakly negatively associated with systemic vascular resistance. Kuroda et al. found that increases in adrenaline correlated negatively with changes in ejection fraction during mental stress. However, other studies have shown that MSIMI was not predicted by the rise in catecholamines in patients with CAD, although Yoshida et al. found a greater increase in norepinephrine in patients with vasospastic angina who developed ST segment depression during mental stress.

This inconsistency in associations between catecholamines and stress-induced responses is mirrored in the effects of β-blockade. Bairey et al. studied the effects of metoprolol or placebo. The impact on MSIMI as defined by wall motion abnormalities was highly variable, with half the patients showing reduced ischaemia while the pattern worsened with metoprolol in a third. In another study, atenolol or nifedipine therapy prevented the fall in ejection fraction found in patients who were positive responders to mental stress, but did not affect ejection fraction in the non-responders.

**Coronary artery vasomotor responses**

Coronary artery constriction and the consequent reduction in myocardial blood flow have been proposed as a cause of MSIMI. Recently, cardiac catheterization studies have used quantitative coronary angiography to assess changes in the diameter of the epicardial coronary arteries during mental stress (see Table 7). These studies confirm that coronary artery vasoconstriction does occur in response to mental stress, but that changes are highly variable. Yeung et al. found that in response to mental stress, there was an average 24% constriction in stenotic areas, a 9% constriction of irregular segments, whereas smooth arterial segments did not change; the result was a variation across imaged segments from 38% constriction to 29% dilatation. Coronary blood flow decreased by 27% during mental stress in patients with stenosed arteries, and rose by an average of 10% in patients with smooth arteries. An association between changes in coronary artery diameter in response to mental stress and acetylcholine was also observed, suggesting a local failure of the endothelium-dependent vasodilatory response. By contrast, stenosed and smooth coronary artery segments showed similar dilatation in response to nitroglycerin, indicating no differences in vascular tone.

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**Table 7** Studies using coronary angiography

<table>
<thead>
<tr>
<th>Author</th>
<th>No. patients</th>
<th>Mental stressor</th>
<th>Medication (on/off)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>L’Abbate et al.</td>
<td>10 CAD</td>
<td>MA</td>
<td>Off</td>
<td>No change in normal or diseased coronary artery segments with mental stress</td>
</tr>
<tr>
<td>Yeung et al.</td>
<td>15 CAD</td>
<td>MA</td>
<td>Not stated</td>
<td>Diseased segments of coronary arteries constrict during mental stress, with dilatation in smooth segments. Responses vary from 38% constriction to 29% dilatation</td>
</tr>
<tr>
<td>Boltwood et al.</td>
<td>12 CAD</td>
<td>Anger recall</td>
<td>Off</td>
<td>Positive correlations between anger responses and coronary vasoconstriction of diseased segments</td>
</tr>
<tr>
<td>Dakak et al.</td>
<td>10 CAD</td>
<td>Computer game</td>
<td>Off</td>
<td>Blood flow measured in LAD artery—none of the patients have significant disease in this vessel. Vascular resistance in LAD decreases during mental stress in controls, but not in CAD patients. Pharmacological interventions suggest an α-adrenoreceptor mediated effect</td>
</tr>
<tr>
<td>Lacy et al.</td>
<td>6 CAD</td>
<td>Speech</td>
<td>Off (although diazepam sedation)</td>
<td>Average 6% decrease in coronary artery diameter during mental stress both in CAD patients and controls</td>
</tr>
<tr>
<td>Kop et al.</td>
<td>59 CAD</td>
<td>MA</td>
<td>Off</td>
<td>18.6% show coronary constriction &gt;0.15 mm during mental stress Coronary blood flow increases in controls but not CAD during mental stress</td>
</tr>
</tbody>
</table>

Mostly men: >75% male participants. MA=mental arithmetic.
There was also substantial variability in coronary vasoconstriction in a larger study in which coronary blood flow was also assessed. Coronary flow velocity increased by 32% with mental stress in controls but not in CAD patients, and 18.6% of patients showed coronary constriction of >0.15 mm. However, responses in the epicardial arteries during mental stress varied between 15% constriction and 27% dilation in diseased segments, and from 22% constriction to 12% dilation in smooth segments. The changes in arterial diameter were associated with the magnitude of diastolic blood pressure stress responses, with vasodilatation in low pressure responders, and vasoconstriction in high diastolic pressure responders.

Kop et al. have argued that the degree of arterial constriction is insufficient to account for the decrease in coronary artery flow measured, and that there is likely to be a significant contribution from vasomotor changes in the microvascular bed. It has been reported that the attenuation in coronary arterial blood flow increase during mental stress can be reversed by alpha-adrenergic blockade through intra-coronary administration of phentolamine. This observation, coupled with the fact that there was no evidence of coronary vasomotion during the study, points to the microvasculature as one area responsible for flow attenuation. Arrighi et al. used PET scanning to quantify myocardial blood flow, and found that coronary flow reserve during mental stress was lower in regions without significant epicardial stenosis than in those with significant stenosis, while the opposite was found during dipyridamole vasodilator stress. This was due to an absolute increase in myocardial blood flow during mental stress in regions with but not without significant stenosis. In healthy controls, both mental and dipyridamole stress induced increased myocardial blood flow. Microvascular dysfunction may be responsible for the blunted myocardial flow response in regions without significant stenosis.

The results of these studies indicate that MSIMI may be sustained by abnormal responses both in the epicardial coronary arteries and in the microvasculature, and that there may be both an impairment of endothelial function and alpha-adrenergic vasoconstrictive responses.

Psychological and central nervous system factors

Surprisingly little is known about psychological aspects of MSIMI. The phenomenon is induced by emotional threat or challenge, but the latter have seldom been quantified. It is not therefore clear whether the tasks that most reliably induce MSIMI are necessarily the most ‘stressful’. The few studies that have assessed subjective responses to tasks have demonstrated positive correlations between increases in anger and anxiety and reductions in left ventricular ejection fraction, and coronary vasoconstriction.

There is some evidence that MSIMI is associated with certain psychological traits. Carels et al. had patients monitor their levels of subjective tension repeatedly in everyday life using diaries, and categorized them into high and low emotional responders. High emotional responders had a greater incidence of wall motion abnormalities compared with low responders on mental stress testing, but emotional responsivity was not linked to myocardial dysfunction on exercise. High emotional responders also had greater trait anxiety and more depressive symptoms, and were more likely to be diabetic and current smokers. No association with hostility was observed. By contrast, another study showed that patients who exhibited MSIMI had higher ratings of aggressive responding, hostile affect, and trait anger than patients who did not show ischaemic responses during mental stress, with no differences in anxiety or neuroticism. Results relating MSIMI with psychological characteristics are therefore inconclusive at present. The cardiovascular responses to mental stress have cerebral correlates as identified using PET scanning, with increased blood flow to the right anterior cingulated gyrus, right insula and cerebellar vermis, and reduced blood flow in the prefrontal and medial temporal cortex in healthy individuals. In one study coupling brain PET scanning with echocardiography, CAD patients who exhibited wall motion abnormalities during mental stress showed heightened regional cerebral blood flow to the left hippocampus and inferior parietal lobe, left frontal gyrus and visual association cortex, and reduced flow to the anterior cingulated and right middle and superior frontal gyri. This suggests that MSIMI may be driven by abnormal patterns of cerebral cortical activation.

Clinical significance of mental stress-induced ischaemia

Association with severity of coronary artery disease

The majority of studies have shown no link between the angiographic severity of coronary...
artery disease and the presence of mental stress ischaemia. Kuroda et al. reported a trend towards greater decreases in ejection fraction during mental stress in patients with three vessel disease, while the rate of MSIMI in Modena's study varied from 54% in patients with one vessel disease to 83% in three vessel disease. However, interpretation of this finding is complicated by the unknown medication status of participants. Studies relating thallium reversibility scores on a prior radionuclide examination with the subsequent incidence of MSIMI have reported variable results. It would appear, therefore, that transient stress-induced ischaemia is not simply a reflection of disease severity, but an indicator of a particular susceptibility to psychological factors.

Laboratory mental stress and ambulatory ischaemia

Ambulatory myocardial ischaemia has parallels with mental stress-induced ischaemia in that both are predominantly silent events, and occur at lower heart rates than exercise-induced ischaemia. They also both occur largely in patients who also experience exercise-induced ischaemia. It has been proposed that mental stress in everyday life is an important determinant of ambulatory ischaemia. Several studies have therefore assessed both MSIMI and ambulatory ischaemia, and have found associations between the two. For example, in the PIMI study, it was found that 49.4% of patients who displayed myocardial ischaemia in response to a speech task in the laboratory had ambulatory ischaemia during Holter monitoring, compared with 34.9% of the remainder. They also experienced more frequent and longer ambulatory ischaemic episodes, but did not show differences in clinical markers of disease severity. The proportions of patients showing ambulatory ischaemia in Legault's series were 68.4 and 37.0% for MSIMI positive and negative groups, and the ejection fraction response to mental stress was a significant predictor of ambulatory ischaemia independent of left ventricular responses to exercise. The frequency and duration of episodes of ambulatory myocardial ischaemia is also predicted by the magnitude of heart rate responses to mental stress tests. Gottdiener et al. compared 24 CAD patients who showed new wall motion abnormalities on mental stress testing with 21 who did not. The duration of ischaemia while the patients were sedentary was 22.9 min in the MSIMI positive group, and 3.6 min in the negative group. In combination, these data suggest that clinical mental stress testing may index triggers of myocardial ischaemia that are also operative in everyday life.

The prognostic significance of mental stress-induced ischaemia

Several of the groups of CAD patients whose sensitivity to mental stress has been evaluated have been followed up to assess the prognostic significance of a positive ischaemic response. All the results published to date have indicated that MSIMI is a predictor of poor prognosis. Specchia et al. tracked 61 patients who showed signs of MSIMI, and 211 who did not, over an average of 51 months. The two groups did not differ in severity of CAD or left ventricular function. Over the follow-up period, 65.5% of the positive mental stress group underwent revascularization (coronary artery bypass surgery or angioplasty), compared with 38.3% in the comparison sample. A 12 month follow-up of 30 high risk patients originally studied using the nuclear VEST found that 60% of MSIMI-positive patients had experienced a non-fatal myocardial infarction, cardiac death or unstable angina requiring hospitalization, compared with 20% of the MSIMI-negative group. Jiang et al. tracked 126 patients over 44 months, and found adverse events (death, non-fatal myocardial infarction or revascularization) in 27.4% mental stress-positive and 11.9% stress-negative patients. The difference was not accounted for by differences in risk profile, and was independent of age, history of myocardial infarction, and baseline ejection fraction. Mental stress-induced ischaemia also predicted adverse outcomes independent of other risk factors over an average 42 months in a group of 79 patients originally tested using radio-nuclide ventriculography or echocardiography. Most recently, the PIMI cohort of 196 patients with CAD was censored after an average of 62 months after mental stress testing. The all-cause mortality rates were 16.2% in mental-stress positive and 6.6% in mental stress-negative patients, a difference that remained significant after adjusting for age, history of myocardial infarction and diabetes, baseline ejection fraction, hypertension, and duration of exercise tolerance tests. Although the numbers of patients followed-up so far are small, current evidence suggests that myocardial ischaemic responses to standardized mental stress are clinically significant, relating both to ambulatory ischaemia and to prognosis.
Limitations in the literature and unresolved issues

As noted in Tables 1–6, mental stress testing has been carried out most commonly in men, and the numbers of women tested has been too small to allow comparisons to be made. Men and women may differ in their cardiovascular responses to mental stress.60 Bairey Merz et al.61 found that women had greater blood pressure, heart rate and rate-pressure product responses to mental stress than men, and that the difference was enhanced among post-menopausal women. It has also been noted that mental stress induced ischaemia is more likely to be associated with chest pain in female than male CAD patients.62 and levels of plasma β-endorphin are also lower. In healthy volunteers without CAD, left ventricular ejection fraction decreases during mental stress were greater in women than men.21 However, there is insufficient information to draw firm conclusions about the prevalence and significance of MSIMI in women with CAD.

An important limitation in the current literature is the lack of data concerning the duration of stress-induced ischaemic responses. In most studies, comparisons have been made between images or measures obtained at baseline, and then during or immediately after mental challenge. Responses may be transient, but it is not clear how long they last. Recent studies indicate that brief mental stress stimulates impairments in vascular endothelial function that last for up to 90 min after the termination of stress.63 Similarly, increases in inflammatory cytokine concentration evolve over several hours.64 It is possible, therefore, that disturbances of myocardial function are also sustained after mental stress tests are completed.

Many of the studies in the literature involve small numbers of patients, and there have been no control groups in several instances. In a number of studies, the controls have been patients under investigation for heart disease; although they were free of CAD, they may have had other cardiovascular conditions, so their results may not have been representative of the healthy population. The preponderance of studies have found evidence of MSIMI, and publication bias in favour of positive results cannot be ruled out.

Finally, there is a growing literature concerning other aspects of psychophysiological response in patients with CAD, highlighting the possibility of differences in stress-related disturbances of autonomic balance,65 endothelial function, and platelet activation.66 These observations have yet to be integrated with research on mental stress-induced ischaemia. Transferring the pathophysiological findings into clinical practice will need more information on both the independent prognostic significance of the mental stress-induced myocardial ischaemia, and the possibility of altering the underlying pathophysiological mechanisms by specific pharmacological or psychological interventions. Such information is currently sparse.

Conclusions

Mental stress induces transient myocardial ischaemia in one third to one half of patients with CAD. Ischaemic responses are induced not by extremely severe emotional stress, but by behavioural challenges similar to those that might be encountered in everyday life, and they are associated with ischaemia on ambulatory monitoring. Mental stress-induced ischaemia is typically without pain, and occurs at lower levels of oxygen demand than ischaemia induced by physical exercise. It is generally not related to the severity of CAD. Stress-induced haemodynamic changes, particularly increases in systemic vascular resistance, coronary artery vasoconstriction, and microvascular changes, may all contribute to the pattern of ischaemia. There is, nonetheless, considerable variability in responses to mental stress that is not understood. No pharmacological interventions have yet consistently blocked mental stress-induced ischaemia. Limited evidence indicates that these stress-induced responses predict adverse coronary outcomes independent of risk factors. It may be premature to advocate that mental stress testing forms an integral part of the routine clinical investigation of patients with suspected or proven CAD, but mental stress testing may provide a means of evaluating the role of emotional factors in acute coronary syndromes and sudden cardiac death.

Acknowledgement

This research was supported by the British Heart Foundation.

References


