ACUTE CORONARY SYNDROMES

Mental stress-induced myocardial ischaemia

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Learning objectives

- Coronary physiology
- The cardiovascular responses to mental and exercise stress
- Triggers of myocardial ischaemia and adverse cardiovascular events

INTRODUCTION

The management of angina is determined by symptoms and cardiovascular risk, together guiding further assessment in order to detect significant underlying coronary artery disease (CAD). The current National Institute for Health and Care Excellence guidelines require that symptoms are precipitated by physical exertion to be defined as typical angina.[1] There are, however, a number of other stressors that may induce myocardial ischaemia, including cold exposure[2] and mental stress. In the first detailed description of angina pectoris in the medical literature in 1772, William Heberden noted "it is increased by disturbance of the mind".[3] Mental stress-induced myocardial ischaemia (MSIMI) is a recognised phenomenon, but in the absence of an evidence base it is not routinely explored during either the clinical consultation or subsequent investigations. Significant uncertainties remain; in particular, how does MSIMI differ from exercise-induced myocardial ischaemia, and does it hold any particular significance for patients with ischaemic heart disease?

MENTAL STRESS AND ADVERSE CARDIAC EVENTS

Numerous observational studies have suggested that exposure to both acute and chronic mental stress is associated with an increased incidence of adverse cardiac events. Natural disasters, including earthquakes[4–7] and hurricanes,[8] have been linked with increases in cardiac mortality immediately after the event. There was a 71% increase in cardiac deaths on the day of the Northridge earthquake and a 35% increase in hospital admissions for myocardial infarction over the ensuing week.[5] Similar findings are reported with unnatural events including in civilian communities under threat of imminent missile attack[9] and with major sporting competitions.[10–13] During the 2006 FIFA World Cup in Germany, the incidence of acute cardiac events was 2.7 times higher on match days involving the German national team.[14] In those known to have pre-existing CAD, the number of cardiovascular (CVS) events increased by a factor of 4, with the highest incidence 2 h after the beginning of each match, suggesting a causal relationship (figure 1). This was driven equally by diagnoses of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and arrhythmia.

Exposure to more mundane mental stress has also been correlated with an increased incidence of adverse cardiac events. Significant increases in the incidence of myocardial infarction have been noted at the start of the working week[15] and around Christmas and New Year.[16 17] In patients with ischaemic heart disease, hostile personality types may also confer a poor prognosis.[18]

ASSESSMENT OF MSIMI

Mental stress-induced cardiac events described above are stochastic events in which coronary atherothrombosis likely plays a major role. Their onset is, therefore, difficult to predict and their pathogenesis in a given individual difficult to study. However, mental stress also induces transient myocardial ischaemia in patients with chronic stable CAD, a more amenable platform for detailed mechanistic research. Mental stress triggers transient myocardial ischaemia in 30–70% of patients with pre-existing CAD[19–26] but is often a silent phenomenon with most patients remaining asymptomatic.[21 22 27–29]

The effect of MSIMI on the heart can be detected using the same non-invasive tests as for exercise-induced ischaemia. These stresses are often compared; consequently, examination of MSIMI has followed the evolution in functional imaging technology.

Initial studies demonstrated MSIMI in patients with known CAD using ST segment depression on the ECG.[30–35] In these early trials, mental arithmetic was the most common mental stressor, although public speaking, anger recall, reaction time and colour-word (Stroop) tasks have since also been employed. MSIMI has been demonstrated using stress echocardiography[36 37] and with imaging methods that directly assess heterogeneity of perfusion including positron emission tomography (PET) and radionucleotide single-photon emission CT (SPECT).[38–40] Echocardiography is an established well-validated method that allows for real-time assessment of a consequence of myocardial ischaemia and a comprehensive assessment of left ventricular (LV) function, while avoiding unnecessary radiation exposure. SPECT, meanwhile, may measure an earlier event in the ischaemic cascade than abnormality of wall motion, but is associated with radiation exposure and therefore does not easily allow for repeat or serial assessments.

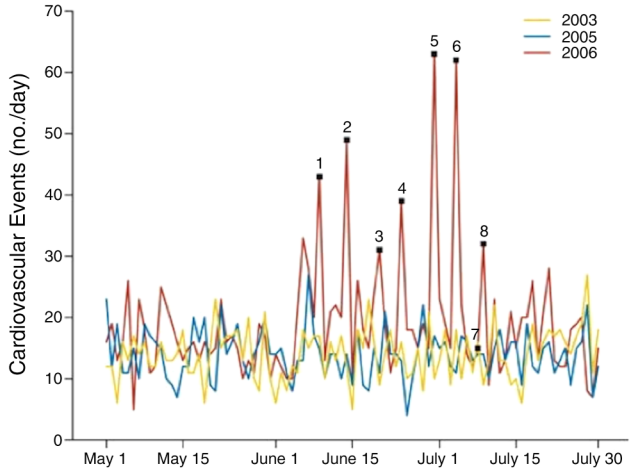

Figure 1 Daily cardiovascular events in the study population from 1 May to 31 July in 2003, 2005 and 2006. The FIFA World Cup 2006 in Germany started on 9 June 2006 and ended on 9 July 2006. The 2006 World Cup matches with German participation are indicated by numbers 1 through 7: match 1, Germany versus Costa Rica; match 2, Germany versus Poland; match 3, Germany versus Ecuador; match 4, Germany versus Sweden; match 5, Germany versus Argentina; match 6, Germany versus Italy; and match 7, Germany versus Portugal (for third-place standing). Match 8 was the final match, Italy versus France. From Wilbert-Lampen *et al*.[14] Copyright 2008 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Early studies suggested that echocardiography may not be as sensitive as other perfusion imaging modalities in detecting MSIMI. In a study by Kuroda *et al*,[40] all patients with established CAD demonstrated reversible perfusion abnormalities but only 50% of these patients had a fall in LV ejection fraction (LVEF) ≥5%. Samad *et al*[41] recently reported a significantly higher prevalence of MSIMI among women compared with men using wall motion abnormalities and LVEF reductions on echocardiography. Surprisingly, York *et al*[42] failed to reproduce these findings in a comparable cohort of females using myocardial perfusion imaging techniques. Samad *et al* argue that perfusion abnormalities identify obstructive coronary disease, whereas wall motion abnormalities are considered a downstream effect of myocardial ischaemia. They propose the higher prevalence of MSIMI in women with ischaemic heart disease (IHD) in their study, as defined by wall motion changes, may reflect mechanisms such as microvascular dysfunction, neurogenic stunning of the myocardium and other catecholamine-related changes that are not necessarily revealed by perfusion assessment.[41] ST-segment analysis appears to be the least sensitive method and is now used in research studies as an adjunct to advanced imaging or as a stand-alone readout during ambulatory monitoring.[30–35]

The reported prevalence of MSIMI varies greatly between studies. This likely reflects differences in the selection of patients, nature of stressor, diagnostic modality and medication status of patients enrolled. Standardisation of both stressor and measurement modality is challenging and limits comparison between studies, although in general following mental stress a fall in LVEF ≥8% or new regional wall motion abnormality (RWMA) has been judged a positive test irrespective of the imaging method.

The majority of patients who display MSIMI also demonstrate exercise-induced ischaemia.[22 43 44] The impact of severity of coronary disease on the extent of MSIMI is not always predictable. Earlier studies suggested an association between fall in global LVEF and extent of CAD.[40] More recently, however, the degree of MSIMI was reported to be independent of the extent or severity of CAD,[45] in contrast to exercise-induced ischaemia. Reductions in global LVEF, without convincing evidence of coincident perfusion deficits or regional wall motion abnormalities,[46] have also been observed in individuals without significant CAD, implying that alternative mechanisms may also exist for cardiac dysfunction during mental stress.

PHYSIOLOGICAL RESPONSES TO ACUTE PHYSICAL STRESS AND ANGINA

Aerobic exercise requires an increase in oxygen delivery to the involved skeletal muscles in order to match oxygen consumption (VO_2). Systemic vascular resistance (SVR) falls due to increased β_2 receptor activation and release of locally acting vasodilators within skeletal muscle. Increased sympathetic activity (predominantly via noradrenaline) and a fall in vagal tone lead to an increase in heart rate (HR) and stroke volume, leading to a rise in cardiac output. These changes necessitate a coincident increase in myocardial oxygen consumption (MVO_2) and delivery.

The major determinant of myocardial oxygen delivery is myocardial blood flow, which is governed by vascular resistance (vessel diameter/tone and collateral flow) and perfusion pressure.[47 48] As flow is maximal during diastole, the proportion of the cardiac cycle occupied by this phase (diastolic time fraction (DTF)) is also important. Perfusion pressure describes the pressure gradient across the microvasculature. At rest the flow distribution across the myocardium is relatively uniform, through local autoregulation of the myocardial resistance vessels.[49] The onset of exercise requires that there is dilatation of both the epicardial coronary arteries and especially the microvascular resistance vessels. This occurs through a variety of mechanisms including local nitric oxide (NO) synthesis and adenosine release. However, transmural microvascular resistance is heterogeneous, with higher minimum resistance (less relaxation) in the subendocardium than the subepicardium. The subendocardium is further disadvantaged by the direction of blood flow, which is from the epicardium to endocardium.[50] Furthermore, during exercise the contractile forces within the heart exert pressure on the microvasculature. These have a disproportionate effect on the subendocardial layer, rendering it more sensitive to ischaemia.[51]

Reduced intracoronary pressure beyond a significant stenosis demands additional dilatation of the microvasculature at rest, to maintain flow. This reduces the capacity for a further fall in resistance in response to exercise. Therefore, the vasodilatory

capacity/reserve, most usually expressed as the ratio of maximal:resting flow, is exhausted prematurely on exercise. Subendocardial resistance is also dependent on HR and increases as the DTF shortens. DTF appears to be the principal factor determining subendocardial perfusion.[52 53] In contrast, subepicardial perfusion is generally unaffected by these changes.[52] Thus, with exercise the imbalance between myocardial demand and flow is greatest in the subendocardium, and when a critical point is reached, ischaemia will ensue.

PHYSIOLOGICAL RESPONSE TO ACUTE MENTAL STRESS IN HEALTHY SUBJECTS

Adaptation to acute mental stress does not require the same increase in VO_2 as response to exercise, and the demands placed on the cardiovascular system are lower. Cardiac output is expected to rise by around 20% from baseline; with a smaller increase in HR, but similar peak systolic blood pressure (BP), to exercise.[54 55] Myocardial oxygen demand, as estimated by rate-pressure product (RPP), therefore, rises with mental stress but to a lesser extent than with exercise. The most marked difference is that SVR increases in response to mental stress,[55] but falls during exercise. Usually, SVR rises steadily during mental stress, progressively increasing LV afterload.[55] This contrasts to the progressive fall in SVR that reduces afterload with physical exertion (figure 2).

The increase in cardiac output, RPP and SVR is mediated by acute rises in circulating levels of cortisol and sympathetic activity. Following mental stress, circulating levels of both adrenaline and noradrenaline increase. There appears to be a greater rise in adrenaline compared with noradrenaline, while the opposite is seen following exercise stress.[56 57] These higher levels of circulating adrenaline lead to systemic vasoconstriction as β_2 agonism is overcome by α_1 activation, causing net vasoconstriction, while myocardial work and oxygen demand are increased by β_1 activation. There is significant interindividual variability in the haemodynamic response to mental stress, with some displaying a predominantly vascular pattern, with more significant increases in SVR than cardiac output, while others show the reverse pattern.[56] The detailed derangements in mediators of vascular tone that underlie these effects are unknown, but acetylcholine and local NO production are implicated, with a blunting of endothelium-dependent vasodilatation following acute mental stress.[58]

During mental stress, the observed increases in adrenocorticotropic hormone (ACTH) and cortisol show significant association with HR and BP response.[55] Release of cortisol during acute mental stress appears to cause endothelial dysfunction within the systemic arterioles, which persists for several hours post-stress and which is prevented by blocking cortisol synthesis.[54] In healthy subjects, cortisol reactivity to acute mental stress has also been associated with decreased total arterial compliance, a measure of vascular stiffness (figure 3).[54]

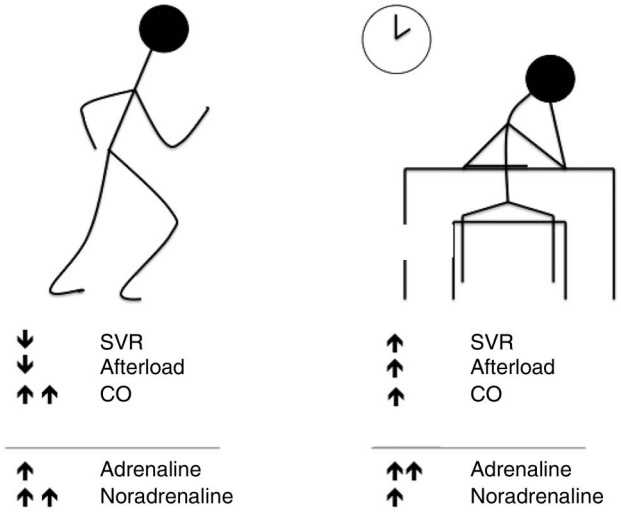

Figure 2 Cardiovascular responses to mental and exercise stress. Exercise is associated with a greater rise in cardiac output (CO). Systemic vascular resistance (SVR) and afterload increase in response to mental stress but fall during exercise. Circulating levels of both adrenaline and noradrenaline increase following exercise and mental stress. Mental stress is associated with a greater rise in adrenaline compared with noradrenaline, while the opposite is seen following exercise stress.

THE ASSOCIATION BETWEEN MENTAL STRESS AND MYOCARDIAL ISCHAEMIA

Increased myocardial work and oxygen demand, higher SVR, rising levels of circulating stress hormones and endothelial dysfunction present a challenging group of overlapping and interacting factors driving MSIMI. Integrating these factors and projecting their effect on the pathological vascular system of patients with ischaemic heart disease may further our understanding of the aetiology of MSIMI.

Increased demand

As noted above, acute mental stress triggers an increase in cardiac output, which in turn increases myocardial work. Hypertension and worsening CAD have been associated with markedly exaggerated increases in BP and HR (so-called cardiovascular reactivity) to mental stress compared with normal controls.[59] The simplest model for MSIMI would, therefore, be similar to that for exertional angina, with rising demand for blood flow exhausting the normal vasodilatory capacity of the myocardium.

If this were the case then, assuming that RPP still reflects myocardial oxygen demand during mental stress, MSIMI should occur at a similar RPP to exertional angina. However, in a given individual, MSIMI occurs at a lower RPP than exercise-induced ischaemia.[22 30 33 36 60] The Psychophysiological Investigations of Myocardial Ischaemia (PIMI) study of 198 patients demonstrated that a stressful speech task produced ischaemia at an RPP of 6800 mm Hg bpm (SD 3500) compared with the mean RPP of 13 200 mm Hg bpm (SD 5400) required to elicit ischaemia on exercise.[36 44] The difference was predominantly driven by the lower peak HR during stressful

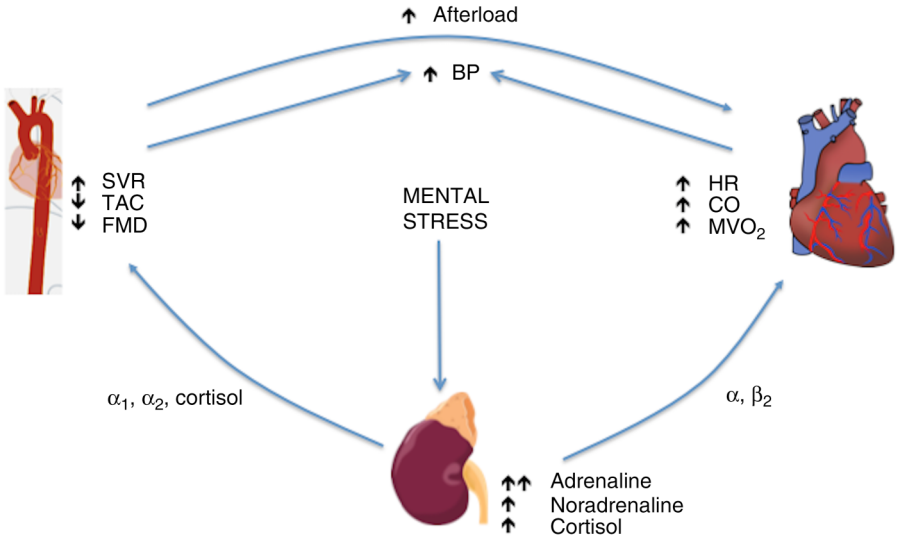

Figure 3 The acute effects of mental stress. Levels of adrenaline increase more than noradrenaline, in contrast to exercise. This leads to increased cardiac output and increased systemic vascular resistance (SVR), increasing blood pressure (BP) and cardiac afterload. α, α-adrenergic receptor; β, β-adrenergic receptor; CO, cardiac output; FMD, flow-mediated dilatation; HR, heart rate; MVO_2, myocardial oxygen demand; TAC, total arterial compliance.

speech. These findings strongly suggest that the mechanisms underlying mental stress-induced ischaemia differ from those triggered by exercise since they consistently occur at a lower RPP, an index of myocardial oxygen demand.

In patients with ischaemic heart disease, development of myocardial ischaemia to mental stress is strongly and negatively correlated with SVR.[36] This is associated with an increase in left ventricular end systolic volume (LVESV), left ventricular end diastolic volume (LVEDV) and stroke volume, demonstrating the effect of an acute increase in SVR on afterload and LV cavity dimensions. These changes increase LV strain, necessitate a greater myocardial wall tension, further compromising endocardial perfusion and promoting the development of ischaemia.

Inadequate supply

As myocardial oxygen demand increases in response to mental stress, in order for ischaemia to ensue there must also be failure of myocardial blood flow to increase to the levels seen during exercise. Further data from the PIMI study[36] suggested that while there was an increase in catecholamine levels during mental stress associated with changes in HR, BP and SVR, these haemodynamic changes alone could not explain the development of MSIMI. A coincident effect of catecholamines preventing increased myocardial flow could provide an explanation.

Myocardial blood flow is dependent on the perfusion pressure across the myocardial vascular bed together with its resistance. Little resistance is generated by the epicardial coronary arteries (conductance vessels) and most by the pre-arterioles and intramyocardial arterioles (the microvasculature). In the absence of a coronary stenosis or significant heart failure causing low systemic BP or high right atrial pressure, dynamic changes in resistance of the vasculature ordinarily allow adequate blood flow across the physiological range. The question is why does this not occur in MSIMI?

THE EPICARDIAL ARTERIES

First to be considered in individuals with ischaemic heart disease is the role of the epicardial arteries. Further to the fixed effects of a stenosis, impaired flow secondary to paradoxical coronary constriction[61–64] may play an important role. Studies using quantitative coronary angiography to assess changes in the diameter of epicardial coronary vessels have confirmed that coronary vasoconstriction does occur in response to mental stress, although these changes seem highly variable.[61–64]

Yeung and colleagues demonstrated a 24% constriction in stenotic, 9% constriction in irregular and no change in smooth, coronary segments in response to mental stress. Coronary blood flow (CBF) decreased by 27% in patients with stenosed arteries and rose by an average of 10% in those with smooth arteries.[61] The vasomotor response correlated with the extent of atherosclerosis in the vessel, suggesting dynamic functional, as well as static anatomical, limitations of flow were responsible.

Substantial variability in coronary vasoconstriction has been reported in a larger study assessing coronary flow.[64] Coronary flow velocity increased by 32% with mental stress in controls but not in patients with CAD. Responses of the epicardial arteries during mental stress varied between 15% constriction and 27% dilatation in diseased segments and from 22% constriction to 12% dilatation in smooth segments.

Endothelial-dependent dilatation in response to increased shear stress is abnormal in diseased coronary arteries due to defective acetylcholine-mediated NO release. Yeung *et al*[61] reported a significant correlation between the vasomotor response to mental stress and the response to acetylcholine. With evidence that both atherosclerosis and mental stress impair NO-dependent endothelial function,[65] these may result in synergistic effects restricting coronary vasodilation. Furthermore, α-adrenergic stimulation resulting from high sympathetic drive may further increase resistance and decrease flow.

MICROVASCULAR DYSFUNCTION

The presence of a significant coronary artery stenosis will require a reduction in the resistance within the dependent myocardium in order to maintain perfusion at rest, limiting coronary flow reserve. In addition, given that MSIMI may also occur in patients with normal epicardial coronary arteries, impaired function of the distal microvascular bed is likely to play a significant role.[66]

Microvascular dysfunction can arise from structural changes in the arterioles, functional abnormalities and external influences. Patients with MSIMI may have altered microvascular structure due to the influence of vascular risk factors (particularly smoking, hypertension and diabetes), as well as previous luminal obstruction by thrombus (see below). The haemodynamic responses to mental stress will also exert additional adverse effects, with increased SVR, reduced DTF and cavity dilation increasing wall stress and external compression of the vascular bed.

Control of microvascular function is more complex than that of the large arteries. The initial pre-arterioles adapt via flow-mediated dilatation in response to shear stress. Dilatation of the more distal arterioles occurs with increased pressure and is sensitive to the direct action of myocardial metabolites. Therefore, the effects of sympathetic stimulation may be more pronounced on the distal microvasculature than on the epicardial arteries. Hence, the attenuated increase in CBF during mental stress can be reversed by alpha-adrenergic blockade using intracoronary phentolamine.[66] Studies with PET[27 67] have also demonstrated reduced coronary flow reserve during mental stress in regions without significant epicardial stenosis, reinforcing the importance of microvascular dysfunction but not indicating its specific cause (figure 4).

CHANGES IN COAGULATION

Acute mental stress has been consistently associated with a procoagulant state through a variety of observations. These include a decrease in plasma volume, an increase in plasma viscosity, changes in a range of clotting factors (VII:C, VIII:C and XII:C, as well as d-dimer and fibrinogen levels),[68] an increased platelet count, enhanced platelet aggregation and an increase in von Willebrand factor.[69 70]

A recent analysis of the baseline data in 269 patients enrolled in the Responses of Myocardial Ischemia to Escitalopram Treatment (REMIT) study demonstrated a significant increase in platelet aggregation in patients who demonstrated MSIMI after a period of mental stress compared with those who had normal LV responses to stress.[71] These platelet abnormalities were present with collagen, serotonin+ADP and adrenaline as aggregatory stimuli, although no specific mechanism was demonstrated. In summary, it would appear that dynamic changes in haemostasis may well play a role in MSIMI and maybe particularly relevant to the stochastic events that cause MI, arrhythmia and death.

CHANGES IN CARDIAC BIOMARKERS

At present, there is no published literature concerning the responses of serum troponin or brain-natriuretic peptide to MSIMI in patients with established CAD. However, Lazzarino *et al*[72] recently reported that exposure to mental stress in disease-free subjects led to an elevation in serum troponin using a high-sensitivity assay, and this was associated with increased levels of salivary cortisol.

THE CLINICAL AND PROGNOSTIC SIGNIFICANCE OF MSIMI

The presence of mental stress-induced ischaemia appears to be a predictor of poor prognosis. While the exact mechanism of mental stress-induced ischaemia is unclear, it is apparent that not all patients with ischaemic heart disease exhibit MSIMI. In patients with ischaemic heart disease, experimentally proven mental stress-induced ischaemia is predictive of ischaemia during ambulatory monitoring[23 29 44 73–75] and of future cardiovascular events.[31 74 76]

The PIMI cohort of 196 patients with CAD were followed up at 62 months following mental stress testing.[76] All-cause mortality was 16.2% in the mental stress-positive group compared with 6.6% in the mental stress-negative cohort. This difference remained significant after adjustment for age, history of MI, diabetes, hypertension and LVEF.

More recently, a meta-analysis of the only five prospective studies investigating the prognostic significance of MSIMI demonstrated a pooled relative risk of 2.24 (95% CI 1.59 to 3.15) for death and/or major adverse cardiovascular events in patients with CAD who exhibited MSIMI versus those who did not.[77] The overall methodological quality was rated as moderately good and there was little heterogeneity between the studies. No further investigation into prognosis has been reported in the literature since this meta-analysis, and this remains a key field for future investigation.

MANAGEMENT OF MSIMI

Recognition of its prognostic importance has fuelled the investigation into specific treatments for MSIMI. The REMIT study was a double-blind trial that randomised 127 patients with stable coronary disease and MSIMI, demonstrated on echocardiography and/or ECG, to either escitalopram or placebo for 6 weeks.[78] At follow–up, more patients taking escitalopram versus placebo had no evidence of MSIMI on rechallenge (34% vs 18%, p=0.04). There was an improvement in LVEF both at rest and after mental stress, as well as decreases in HR and RPP during the mental stress protocol in the treatment group. The positive effects of Escitalopram observed may be due to reduced platelet aggregation[79] or a downstream effect of modification of central and peripheral serotenergic function.[78]

A number of limitations of this study have been highlighted by the trial investigators. Fifteen subjects withdrew during the study (eight in the

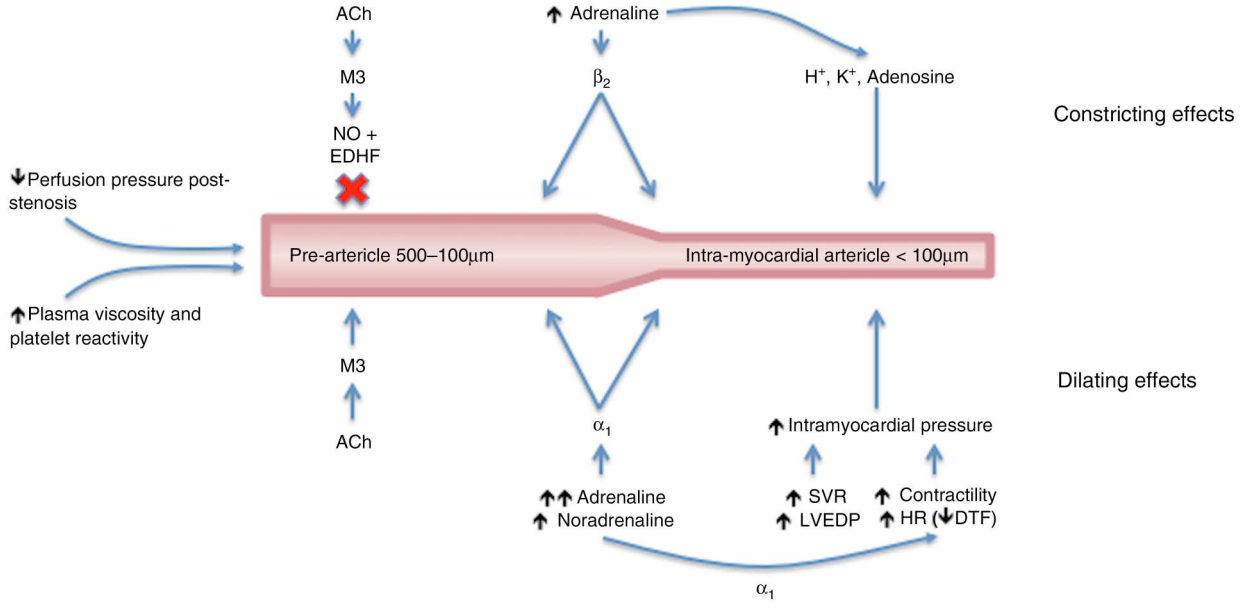

Figure 4 The effects of mental stress on the coronary microcirculation. Failure of normal stress-induced nitric oxide (NO)-mediated vasodilatation leads to unopposed acetylcholine (ACh) muscarinic acetylcholine receptor (M3)-mediated vasoconstriction in the pre-arteriolar vessels. In addition, more significant release of adrenaline activates α_1 as well as β_2 receptors leading to net vasoconstriction. Finally, intra-myocardial pressure rises and plasma viscosity increases, leading to reduced flow. α, α-adrenergic receptor; β, β-adrenergic receptor; DTF, diastolic time fraction; EDHF, endothelial-derived hyperpolarising factor; LVEDP, left ventricular end diastolic pressure; SVR, systemic vascular resistance.

escitalopram group and seven in the placebo group). Given the modest size of the study and intention-to-treat analysis, this number of dropouts could have impacted the findings. Furthermore, this study did not address whether reductions in MSIMI at 6 weeks reached the ceiling effect and was not designed to investigate the effects of Escitalopram on major adverse cardiovascular events. There is currently insufficient evidence to recommend SSRIs in all patients with MSIMI. However, this presents an exciting avenue for further investigation. Further larger trials are needed to explore the mechanisms accounting for these results and to determine whether similar or longer-duration interventions may impact upon major adverse cardiovascular events.

As with all patients with ischaemic heart disease, the role of non-pharmacological interventions must not be overlooked. Blumental and colleagues described a cohort of 107 patients with MSIMI and randomised them to stress management classes, exercise classes or usual medical care.[80] Stress management classes were associated with a significant reduction in death, non-fatal myocardial infarction or revascularisation compared with usual medical care during a mean follow-up of 38 months. Interestingly, the investigators also demonstrated a reduction in cardiovascular and cortisol response to mental stress in healthy controls following a period of exercise training, suggesting a protective role for exercise.[57]

A small, randomised crossover study of 15 patients compared nifedipine, atenolol and placebo in patients with documented MSIMI using radionucleotide ventriculography to assess global and regional LV systolic function.[37] In a subset of five patients who had a fall in LVEF of >5% following mental stress, administration of either nifedipine or atenolol led to the maintenance of resting systolic function. The only other supporting research is from a small study where patients were randomly assigned to propanolol, with or without aspirin coadministration. Propranolol prevented an increase in von Willebrand factor in response to mental stress.[69] The only study to examine the role of ACE inhibitors in MSIMI was a retrospective analysis of 218 patients with stable CAD who underwent testing for MSIMI.[81] The authors reported that patients who were prescribed an ACE inhibitor were less likely to have demonstrable MSIMI via SPECT (OR 0.42), though they acknowledged significant limitations in the study.

Despite the lack of evidence for specific therapies benefiting patients with MSIMI, it must be remembered this pathological condition is both silent and prevalent and thus would have been present in a significant proportion of patients enrolled in the landmark studies of secondary prevention of ischaemic heart disease to date. ACE inhibitors, statins and β-blockers reduce SVR, sensitivity to sympathetic drive and myocardial work. In addition, they may contribute to improved endothelial function. Their use should, therefore, remain the central pillar of management for all patients with IHD and MSIMI. An important increasingly recognised phenomenon is that of patients presenting with non-obstructive coronary disease and chest pain with ischaemia. Further investigating the mechanisms of MSIMI may help to shed light on this clinical presentation and interesting patient cohort.

CONCLUSIONS

Mental stress-induced ischaemia has been demonstrated in patients with and without significant CAD and is often a silent phenomenon. It occurs at lower levels of cardiac work than exercise-induced ischaemia and is less tightly correlated to the severity of CAD. There is considerable individual variability in the response to mental stress that is not understood. Sympathetic activation, increased SVR, coronary constriction and microvascular dysfunction may all play an important role in the pathogenesis. While limited evidence indicates mental stress-induced ischaemia predicts adverse coronary outcomes independent of risk factors, no pharmacological interventions have yet consistently blocked MSIMI and a role for its routine clinical assessment is yet to be established. Although it seems likely MSIMI is the cause for adverse outcomes, it could merely be a marker of susceptibility. Consequently, providing established secondary prevention therapies to this patient group must remain the priority as investigation for targeted drug treatments continues.

Contributors All authors have been involved in drafting the manuscript. Furthermore, all authors have approved the manuscript and agree with its submission.

Competing interests None declared.

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Key messages

- Mental stress is associated with an increased rate of cardiovascular events in the general population.
- Ischaemia induced by mental stress is commonly asymptomatic.
- In patients with coronary artery disease, mental stress-induced myocardial ischaemia (MSIMI) occurs at lower levels of myocardial work than exercise-induced ischaemia and conveys a worse prognosis.
- Large increases in adrenaline and cortisol levels are associated with increases in systemic vascular resistance, which increases myocardial oxygen demand.
- Myocardial blood flow is impaired by microvascular dysfunction and extravascular compression.
- SSRIs present an interesting targeted therapy for MSIMI, but usual secondary prevention is the cornerstone of management.
- Regular exercise and stress management should be encouraged in all patients with ischaemic heart disease at high cardiovascular risk.

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