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Current Perspective on Mental Stress–Induced Myocardial Ischemia

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Abstract

Mental stress and emotional arousal can act as triggers of myocardial infarction and other adverse cardiovascular outcomes. This editorial presents an overview of the research on mental stress–induced myocardial ischemia (MSIMI) and comments on two investigations examining MSIMI published in this journal. These studies confirm that MSIMI is frequently observed in patients with coronary artery disease and that characteristics, such as being a woman younger than 50 years and depression, may increase the relative risk of MSIMI. The method used for determining MSIMI (i.e., assessing cardiac function as determined by echocardiography versus measurement of myocardial perfusion using single-photon emission computed tomography), as well as the nature of the mental stress protocols (i.e., one stress task versus several repeated tasks), may have important effects on the findings of MSIMI research and on their interpretation. An overview of clinical characteristics of MSIMI is presented, and the article concludes with possible directions for future MSIMI research.

Keywords

myocardial ischemia; mental stress

Progress in science is often driven by developments in technology and methodology (1), with individual observations leading to scientific hypotheses that can be tested using systematic research methodologies. As our understanding increases, hypotheses and research methodologies are refined. Such is the case with our understanding of the relationships among stress, emotion, and cardiac outcomes. Early observations suggested that intense emotions could be a powerful trigger of angina pectoris and, indeed, myocardial infarction (2). Case reports and clinical research conducted in the 1960s demonstrated that electrocardiographic (ECG) changes indicative of a decrement in cardiac function could be provoked by mental stress in patients with coronary artery disease (CAD) (3). Testing the effects of physical stress—for example, exercise—on cardiac function is a hallmark diagnostic approach for identifying obstructive CAD. Mirroring this approach, researchers, over the past three decades, have sought to assess the effects of psychological or mental stress in much the same way.

One aspect of cardiac function that has drawn particular research attention is myocardial ischemia, defined as an imbalance between myocardial oxygen demand and supply In the typical scenario, this imbalance is caused when an increase in demand consequent to physical stress comes up against a limitation in myocardial blood flow consequent to an obstructive stenosis. Yet, this imbalance is also observed during mental or psychological stress, a phenomenon called *mental stress induced–myocardial ischemia* (MSIMI). This editorial is a commentary on two articles in *Psychosomatic Medicine* that have looked at MSIMI—an article in this issue by Vaccarino and colleagues (4) and a recent article by Boyle et al. (5). Several similarities and differences between these studies are worth noting here. We also comment more generally on the body of research investigating MSIMI.

Boyle et al. (5) used left ventricular (LV) dysfunction as the measure of MSIMI in a sample of more than 300 predominantly older white men (82% male and white; mean age = 62 years) with coronary heart disease and demonstrated that depression symptom severity (based on the Beck Depression Inventory) predicted the occurrence of MSIMI and the number if stressor tasks during which MSIMI was observed. By linking depression to the occurrence of MSIMI, these investigators provided evidence consistent with the hypothesis that at least part of the risk of cardiac event recurrence and mortality associated with depression may be attributable to MSIMI. These investigators also found that a higher percentage of patients developed LV dysfunction with mental stress than with exercise stress (44.2 % versus 33%). The sample was heterogeneous, including patients with angiographic findings of coronary obstruction, along with those having a history of myocardial infarction, and/or prior coronary or surgical revascularization. Thus, it is noteworthy that although some study participants may not have had a coronary obstruction sufficient to cause LV dysfunction with exercise stress—or to warrant percutaneous intervention—they nonetheless developed LV dysfunction with mental stress. These findings therefore suggest a potential clinical value of mental stress versus physical stress for the determination of risk.

In a study reported in this issue of *Psychosomatic Medicine*, Vaccarino and colleagues (4) assessed sex differences in exercise-provoked ischemia and MSIMI, using single-photon emission computed tomography myocardial perfusion imaging (MPI) as the measure of ischemia. Compared with Boyle et al. (5), the sample was relatively young (age, 38–60 years) and comprised post-MI patients (49 men and 49 women). In contrast to Boyle and colleagues, Vaccarino et al. observed a slightly higher overall prevalence of exercise-induced ischemia than MSIMI (36% versus 25%). More importantly, they observed a higher prevalence of MSIMI in women younger than 50 years compared with age-matched men (52% versus 25%). In contrast to Boyle et al. (5), those demonstrating MSIMI were predominantly younger, obese, and African American, with relatively low socioeconomic status. As noted by the investigators, the prevalence of MSIMI among these younger women may be attributable to female-specific pathophysiological mechanisms involving coronary reactivity and microvascular function, something more likely to be observed with the flow-based assessment of MSIMI used here. The nature of the sample also raises potential elements of risk for MSIMI. For example, obesity is associated with higher circulating levels of proinflammatory cytokines, which has also been linked to MSIMI when assessed by MPI (6). Another possible factor is the high burden of psychosocial risk seen in the younger women in their sample, who were more often poor, of minority race, with a history of sexual

abuse, and with higher levels of depressive symptoms. These more chronic stress factors may be part of a vulnerability spectrum that contributes to a psychological or physiological susceptibility to acute stress, particularly when the measure of ischemia relies on myocardial blood flow directly, and thus may provide a window on dynamic coronary vasomotor activity. Indeed, these findings highlight an additional, methodological difference between Boyle et al. and Vaccarino et al. that has important implications for MSIMI research moving forward.

In one of the earliest studies of MSIMI, Deanfield et al. (7) demonstrated, in a small sample of patients, that a significant decrement in myocardial blood flow was induced by the performance of a demanding mental arithmetic task, although ECG changes and angina symptoms during arithmetic stress were relatively rare. These findings suggested that the pathophysiology underlying MSIMI likely differed from that underlying exercise-provoked ischemia. Most studies since then have also shown that MSIMI—regardless of how it is measured—also occurs at a lower myocardial oxygen demand than exercise-induced ischemia. As the field developed, the more precise demonstration of ischemia by myocardial blood flow moved to the assessment of ventricular performance as the measure of ischemia (e.g., changes in LV wall motion or ejection fraction), as this was more widely used in cardiology practice and provided for repeated testing using multiple consecutive mental stressors (8). This is the approach taken by Boyle et al., which allowed them to use multiple mental stress tasks, whereas Vaccarino et al. could assess MSIMI in response to only one stress task. What followed was a series of studies by various research groups (estimated at more than 34 studies as of 2003) (9), including the National Heart, Lung, and Blood Institute–funded Psychophysiological Investigations of Myocardial Ischemia multisite investigation (10), each of which demonstrated MSIMI in 30% to 70% of heterogeneous patient samples with stable CAD (9,11). The results of these studies also pointed to aspects of pathophysiology and risk, highlighting to various degrees the risk imparted by hostility and anger, and the comparability of ventricular dysfunction in the laboratory to ECG changes during daily life stress (12). **Table 1** provides a summary of the characteristics of MSIMI identified by the current body of research in this area.

Although many studies have shown that LV function measured by, for example, echocardiography can be used to assess MSIMI (e.g., Ref. (13)), such measures have problems related to sensitivity and specificity, when compared with assessment of MSIMI using MPI. This may not be surprising because mental stress induces an increase in peripheral vascular resistance and thus afterload, and so a decrement in LV function may merely reflect an increase in the pressure against which the LV must pump, rather than any reduction in myocardial blood flow, that is, myocardial ischemia. Studies of myocardial blood flow with mental stress have also demonstrated a significant flow decrement in coronary distributions without flow-limiting atherosclerotic plaques and significant coronary vasoconstriction in coronary segments with only minor obstructions (14,15). This research points to a dynamic coronary obstruction—for example, significant vasoconstriction—during mental stress. Therefore, MSIMI assessed by LV dysfunction may not be as reliable as findings obtained using measures of myocardial perfusion.

Also of note is recent research showing that mental stress induced with the same stressors used in MSIMI research also provokes endothelial dysfunction, with dynamic vascular effects lasting up to 90 minutes after cessation of the stressor. Mental stress–provoked endothelial dysfunction may in part underlie MSIMI. This line of research thus calls into question the notion of using serial mental stress tasks in the study of MSIMI, as in Boyle et al., because of the potential for cumulative effects after repeated exposures. Therefore, although using only one stress task as in Vaccarino et al. raises the issue of stress "potency" of the particular task chosen for each participant in a study of MSIMI, the findings of studies using multiple stressors as in Boyle et al. raise issues of interpret-ability because of possible carryover effects.

New developments in the understanding of the pathogenesis of CAD suggest that acute coronary syndromes may result from the confluence of multiple factors that can give rise to atherosclerotic plaque rupture and the thrombotic cascade (16). The articulated model underscores the importance of factors that cause an increase in coronary vasomotor tone, including stress, depression, and endothelial dysfunction. This perspective emphasizes that a perturbation in vascular performance and consequent reduction in myocardial blood flow, such as has been observed during mental stress, can increase the likelihood of coronary constriction and atherosclerotic plaque rupture. It furthermore suggests that rather than a focus on myocardial ischemia, future research directed at understanding the link of mental stress to cardiovascular prognosis and acute coronary syndromes would benefit from a greater emphasis on coronary vascular function.

The articles by Vaccarino et al. (4) and Boyle et al. (5) support the notion that methodology affects the results of research in this area and contributes to the generation of new hypotheses. At the same time, these two studies increase our understanding of, and provide further evidence that important psychosocial factors—poverty, sexual abuse, and depression—are transduced into health-relevant outcomes. As in the past, research directed at understanding the effect of mental stress on coronary atherosclerosis and its clinical manifestations—myocardial infarction and ischemia—continues to evolve. Selection of research paradigms and measurement methodologies chosen to further the understanding of the links among stress, depression, sociodemographic characteristics, and other psychosocial factors would benefit from designing research studies that are based on new understanding of the pathophysiology of atherosclerosis. This would include, for example, the autonomic factors that contribute to dynamic coronary vasomotor tone and obstruction, and the novel technologies such as multibeam computed tomography angiography and cardiac magnetic resonance, that are being developed to measure the associated disease processes.

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Glossary

CAD	coronary artery disease
ECG	electrocardiogram

LV	left ventricular
MI	myocardial ischemia
MSIMI	mental stress–induced myocardial ischemia.

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TABLE 1.

Characteristics of Mental Stress–Induced Ischemia

Observed in 30%-70% of patients with coronary artery disease
Rarely detectable with ECG in the laboratory
Requires myocardial functional or perfusion imaging (echocardiography, SPECT, PET, cardiac MR)
Often asymptomatic (silent ischemia)
More common in patients with exercise-inducible ischemia than in patients without exercise-induced ischemia
Effects in the laboratory vary in their reproducibility.
Associated with ambulatory ischemia
Occurs at lower heart rate (i.e., lower cardiac demand) than with exercise
Reduced coronary supply plays an important role.
Mental stress–induced ischemia is associated with poor prognosis and increased risk of mortality.

ECG = electrocardiogram; SPECT = single-photon emission computed tomography; PET = positron emission tomography; MR = magnetic resonance.