Mental stress as a trigger of acute cardiac events: the role of laboratory studies

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Mental stress has long been implicated as a potential trigger of myocardial infarction and sudden cardiac death. This article reviews research conducted in the past two decades utilizing laboratory studies to investigate behaviorally-induced pathophysiological effects (including increased cardiac demand, decreased myocardial supply, and impaired dilation of coronary resistance vessels), in patients with coronary artery disease. The clinical significance of mental stress-induced ischemia is supported by findings of a predictive relationship of mental stress-induced ischemia for ambulatory ischemia and subsequent cardiac events. Mental stress-induced ventricular fibrillation, ventricular tachycardia, and T-wave alternans are also being explored as possible markers of arrhythmic vulnerability in human and animal models. T-wave alternans comparable to exercise can be induced by an anger-like state in an animal model, and with mental stress in patients with implantable cardioverter-defibrillators. Future directions for research on mental stress and cardiac events are suggested, including further studies of mechanisms of mental stress-induced arrhythmia and ischemia, additional studies of the prognostic significance of stress-induced ischemia and T-wave alternans, and use of pharmacological and psychosocial treatments for preventing stress-induced cardiac events.

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Until recently, evidence for the role of mental stress as a trigger of myocardial ischemia, infarction, and sudden cardiac death has been based on case reports, epidemiological research, and human and animal studies demonstrating the effects of mental stress on the cardiovascular system. Although observational epidemiologic studies can point to associations between stress and coronary artery disease (CAD) events, they do not reveal mechanisms by which psychosocial stress can affect the onset and course of CAD.

In the past decade, studies have utilized a variety of techniques to assess cardiac function in the laboratory and have provided convincing evidence for the pathophysiological effects of behavioral factors as triggers of myocardial ischemia. Although the endpoints of primary importance for the prevention of cardiovascular disease include myocardial infarction, unstable angina, and sudden cardiac death, research on ischemia and malignant arrhythmias has provided a pathophysiologic model for understanding mechanisms by which mental stress may trigger clinical events. In this short paper, we will touch on two issues derived from laboratory research on mental stress-induced ischemia: 1) the prevalence and pathophysiology of mental stress ischemia; and 2) the clinical implications (if any) of acute mental stress testing and mental stress ischemia.

Prevalence and characteristics of mental stress-induced ischemia

Ambulatory ECG monitoring studies suggest that, during daily life, a variety of physical and mental activities are associated with the occurrence of ischemia, and mental activities are almost as potent as physical activities in triggering daily-life ischemia. In the past decade, studies have utilized a variety of more sensitive noninvasive means (e.g., radionuclide ventriculography, positron emission tomography scanning, thallium perfusion imaging, and two-dimensional echocardiography) for evaluating the effects of mental stress on myocardial ischemia. These studies have revealed that laboratory mental stressors can provoke ischemia in a substantial subset (30-70%) of CAD patients[1,2]. This ischemia is usually silent, is rarely accompanied by ECG evidence of ischemia, and occurs primarily among patients with evidence of exercise-inducible ischemia.

Pathophysiology

Although mental stressors produce reliable increases in heart rate and blood pressure, the magnitude of heart rate responses is usually much less during mental stress than during exercise in the same patient. Blood pressure changes, however, are comparable between exercise and mental challengers[2]. The significant blood pressure responses produced by mental stressors raise the possibility that elevated myocardial demand contributes to stress-induced ischemia. In this regard, patients who experience mental stress-induced ischemia also have greater blood pressure responses to stress than do CAD patients without ischemia[3,4].

Since the heart-rate blood-pressure product at onset of mental stress-induced ischemia is markedly less than that for exercise ischemia, a primary reduction in myocardial oxygen supply might also be operative during mental stress-induced ischemia. For example, Yeung et al.[5] observed a constriction of epicardial atherosclerotic coronary segments in response to mental stress, providing supportive evidence that myocardial blood supply may be reduced during mental stress. However, this study did not find a significant reduction in epicardial coronary blood flow, suggesting that mental stress ischemia could not be attributed to epicardial constriction alone. Dakak et al.[6] also investigated coronary microcirculation responses to mental stress and observed that the coronary arteries of normal patients dilated during mental stress, but in patients with mild CAD, there was evidence of impaired dilation of coronary resistance vessels. More recent research has presented a somewhat more complex picture. For example, Kop et al.[7] corroborated the finding of failure to increase coronary flow responses to mental stress in CAD patients. However, coronary constriction with mental stress occurred in only a minority (< 20%) of CAD patients. Interestingly, in this study, vasoconstriction in angiographically diseased arteries was positively related to magnitude of hemodynamic responses to mental arousal. Thus, combined increases in cardiac demand and concomitant reduced myocardial blood supply may contribute to myocardial ischemia with mental stress.

Clinical significance

Although the aggregate results of numerous studies indicate that mental stress can induce wall motion abnormalities and reduce ejection fraction in a sizable subset of CAD patients[8-10], several aspects of these data raise questions regarding the clinical significance of mental stress-induced ischemia. Deedwania[11] has noted that, unlike exercise-induced ischemia, most episodes of mental stress-induced ischemia are brief in duration, asymptomatic, and of lesser magnitude in terms of ischemic severity. It should be noted that the sample sizes in these studies are relatively small, and future research is needed to confirm these observations.

The possible clinical significance of ischemia elicited by mental stress testing is bolstered by three recent studies that reveal a correspondence between ischemia induced by mental stress and ambulatory ischemia assessed during daily life. In one study, Gottdiener et al.[8] observed that in CAD patients, ischemic wall motion abnormalities during laboratory-induced mental stress testing were predictive of increased risk of ischemia during sedentary activities of daily life. These findings have been corroborated by two other studies[3,12].

Prognostic significance of mental stress-induced ischemia

Additional evidence for the clinical importance of mental stress-inducible ischemia comes from recent observations that it predicts subsequent clinical events in patients with CAD[3,8,13,14]. The clinical significance of exercise testing as a predictor of prognosis has been well established, and ambulatory ECG studies have shown that patients with daily life ischemia have a worse prognosis when compared to those who do not manifest ischemia[15,16]. For example, Jiang et al.[17] prospectively followed 126 patients with stable angina who underwent mental stress and exercise testing using radionuclide ventriculography. Twenty-eight patients (22%) experienced at least one clinical event (cardiac death, myocardial infarction, coronary artery bypass grafting, angioplasty) over an average follow-up of 3.2 years. Interestingly, mental stress ischemia, defined in terms of a transient decrease in ejection fraction of > 5%, was associated with a nearly 3-fold increase in clinical events. This effect remained significant even after controlling for risk factors and for exercise ischemic responses. At least two other research groups have corroborated the additional prognostic significance of mental stress ischemia among CAD patients with prior positive exercise tests, and found a 2-fold increased risk for clinical events in patients with mental stress-induced ischemia[18,19]. Finally, Sheps et al.[20] recently noted that the presence of mental stress ischemia was predictive of subsequent cardiac death in stable CAD patients.

Laboratory assessment of cardiac electrical instability

In addition to studies of myocardial ischemia, recent developments in technologies for measuring cardiac function in the laboratory and during daily life provide an opportunity for research linking mental and physical stress to the triggering of malignant arrhythmias in vulnerable patients with coronary disease. These developments include the validation of techniques for quantifying electrocardiographic markers of

vulnerability to ventricular fibrillation and ventricular tachycardia in cardiac patients; and the use of implantable cardioverter-defibrillators (ICDs) in survivors of life-threatening arrhythmias. These techniques may make it possible to identify and study individuals at risk for future arrhythmic episodes.

Several investigations have demonstrated that electrocardiographic T-wave alternans, an index of beat-to-beat variation of T-wave morphology, is a powerful predictor of future arrhythmic events in vulnerable patients, including patients with ICD and patients referred for electrophysiological testing[21-23]. T-wave alternans levels increase significantly in response to exercise, and the magnitude of alternans responses to exercise is related to adverse clinical outcomes in patients with known arrhythmic vulnerability[24-30]. Other clinical conditions associated with elevated T-wave alternans include acute ischemia[31,32], myocardial infarction[33], and long QT syndrome[34,35]. The effects of mental stress on T-wave alternans may be an important risk stratifier in individuals with CAD and documented vulnerability for life-threatening arrhythmias[36].

Human and animal studies have also demonstrated that emotional arousal can induce ventricular arrhythmias and uncover latent arrhythmic vulnerability[37]. Mental stress testing in non-sedated patients undergoing electrophysiological testing results in shortened cycle lengths during pacing and ventricular tachycardias that are resistant to termination[38]. Kovach et al.[39] have recently demonstrated that provocation of an anger-like state in canines increases arrhythmic vulnerability in the form of T-wave alternans to a magnitude comparable to ischemia induced by acute coronary artery occlusion.

Recently, we investigated whether arrhythmic vulnerability in the form of increased T-wave alternans responses can be uncovered in response to mental stress in 18 patients with CAD. Alternans responses of the ICD patients were compared to those of matched controls. Also assessed were differences between mental stress and exercise-induced T-wave alternans responses, and the relationship of heart rate changes to stress-induced alternans. We observed that an increase in T-wave alternans was inducible with mental stress (anger arousal and mental arithmetic) in coronary disease patients with ICDs. After correcting for heart rate increases, alternans was more pronounced with mental stress than exercise[40]. In addition, ICD patients showed more stress-induced alternans than matched normal controls. We also demonstrated a mental stress-induced increase in QT variability[41].

Future directions

Laboratory research has demonstrated that mental stress can act as a trigger of myocardial ischemia and can also elicit latent cardiac electrical instability in vulnerable patients with CAD. It is possible to speculate that mental stress may be comparable in importance to strenuous physical activities as a trigger for clinical events because patients with CAD engage in strenuous exercise only infrequently. Accordingly, the following priorities are identified for further research:

• The mechanisms involved in both mental stress-induced ischemia and stress-induced vulnerability to cardiac arrhythmias warrant further investigation. Triggering effects of mental stress-induced ischemia may be related both to increased cardiac demand, resulting from hemodynamic challenge, and failure to increase myocardial blood flow during stress and/or epicardial coronary vasoconstriction. Most of the attention in the literature has assessed epicardial constriction and blood flow changes. However, results in this area have been inconsistent and have presented a more complex pathophysiologic picture[6,7], and further investigations of coronary microcirculation responses to mental stress are warranted;

• Further research is also needed to assess the potential prognostic significance of mental stress-induced ischemia and/or cardiac electrical instability. Existing prognostic studies suffer from several limitations, namely, the populations studied are limited to CAD patients with prior positive exercise tests, the sample sizes are relatively small, and the samples experienced relatively few endpoint events. For example, recently we have observed that mental stress ischemia is highly prevalent in patients with reduced ejection fractions and vulnerability to cardiac arrhythmias. Clearly, future studies of larger and more diverse patient groups are needed to assess adequately the prognostic and/or clinical significance of vulnerability to mental stress;

• with respect to studies of stress-induced T-wave alternans and cardiac electrical instability, the incremental clinical utility, if any, above the risk assessed by exercise-induced alternans remains to be determined. The mechanisms of mental stress-induced ventricular arrhythmias are not well understood, and may involve direct neurocardiac pathways as well as indirect effects of ischemia induced by mental stress. Thus, the neural and/or endocrine mechanisms of ischemia in mental stress-induced alternans and the role of ischemia in inducing stress alternans also warrant attention;

• More work is needed to assess pharmacologic and non-pharmacologic means for preventing the triggering of clinical events by mental stress. One study[42] observed that beta-adrenergic blockade might be only partially beneficial in treating ischemia triggered by mental stress. However, another report observed that beta-blockers and calcium channel blockers were both effective in reducing mental stress ischemia[43]. In addition, a recent epidemiologic study[44] observed that triggering of myocardial infarction by mental stress was less evident in patients taking aspirin. Such findings suggest that the antiplatelet effects of aspirin can moderate the triggering effects of mental stress.

An alternative or adjunctive, non-pharmacologic treatment approach such as psychosocial treatment or behavior therapy may also prove useful in reducing the adverse consequences of mental stress in triggering cardiovascular events. In this regard, Blumenthal et al.[45] observed that a stress-reduction program in CAD patients with documented ischemia was effective in reducing mental stress ischemia and subsequent clinical events over the course of a 2-year follow-up study period.

Concluding comment

The fact remains that psychosocial stress is pervasive and often unavoidable. Therefore, further research on pathophysiological mechanisms mediating the associations between acute stress, myocardial ischemia, and cardiac electrical instability, as well as on possible moderators of this association must remain a priority of behavioral cardiology research.

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