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The heart-brain interaction during emotionally provoked myocardial ischemia:

Implications of cortical hyperactivation in CAD and gender interactions

Stress has been defined as a state of threatened homeostasis that is reestablished by physiologic adaptive responses. If the adaptive responses are inadequate or excessive and prolonged, homeostasis is not attained and pathology ensues.[1]

Among the pathologies that are related to stress and its associated emotional manifestations is coronary artery disease (CAD). It has been established by multiple laboratories that 30% to 50% of CAD patients exhibit transient, symptomless myocardial ischemia during mental stress performed in a laboratory setting.[2–4] The clinical manifestations of this mental stress-induced ischemia include profound left ventricular dysfunction[5,6] and the triggering of acute coronary syndrome[7] and potentially fatal arrhythmia.[8,9] Furthermore, up to 75% of ischemic episodes seen during ambulatory electrocardiographic monitoring in patients with chronic CAD occur during routine daily activities that carry a considerably lower metabolic demand than is required to provoke ischemia during exercise diagnostic testing.[10] Furthermore, these ischemic episodes occur without symptoms.[10] This ischemia in response to emotional provocation differs from exercise-induced ischemia with regard to several pathophysiologic determinants and clinical presentation.

Among patients with CAD, exercise has been shown to initiate various homeostatic responses and attendant changes in myocardial blood flow and ventricular function that are indices of myocardial ischemia. Emotional provocation with the attendant cognitive demand is associated in the brain with activations in regions involved in processing of cognitive stimuli. Simultaneous with these activations in regions known to be involved with cognitive and emotional function are activations of the effectors responsible for cardiovascular physiologic funtion. Accordingly, studies of the brain during emotional provocation that culminates in myocardial ischemia are cardinal to our understanding of ischemic clinical presentations.

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MENTAL STRESS VS EXERCISE STRESS

The physiologic responses to mental stress and exercise stress differ in several important ways. For example, exercise produces a substantially greater increase in heart rate and a somewhat greater increase in systolic blood pressure compared with mental stress, largely as a function of the increased metabolic demands associated with exercise stress.[2] Diastolic blood pressure and systemic vascular resistance, which rise with mental stress, are flat or decrease in response to exercise.[11] In patients with CAD, angina accompanies ischemia provoked by exercise stress, particularly when the level of exercise stress approaches maximal exercise capacity. Angina, however, occurs rarely during ischemia provoked by mental stress.

In 1984, Deanfield et al measured uptake of rubidium-82 with positron emission tomography (PET) after mental arithmetic challenges and again after physical exercise in 16 patients with chronic stable angina.[12] After mental arithmetic, 12 of the 16 patients had regional perfusion abnormalities but only 6 had ST-segment depression and 4 had an anginal episode. Six patients with perfusion abnormalities had neither angina nor ST-segment changes. Subsequent research in a number of laboratories has served to highlight several important pathophysiologic elements that distinguish mental stress-provoked ischemia, most notably an apparently primary role for dysfunction in the epicardial vessels[13] and microvascular bed.[14]

Mental stress-induced ischemia carries poor prognosis

Clinical studies have demonstrated the negative prognostic impact of mental stress-induced myocardial ischemia. Patients with a perfusion deficit on PET, or left ventricular dysfunction on echocardiog-

raphy, when subjected to laboratory mental stress are at increased risk for subsequent myocardial infarction, unstable angina, and revascularization[15–17] and have a greater 5-year mortality than those patients who do not demonstrate this ischemic response.[4] Treatment strategies tailored to patients with stress-induced myocardial ischemia (ie, cognitive behavioral therapy and stress management) decrease the incidence of cardiovascular events compared with usual care.[18,19]

New approaches needed for ischemia from mental stress

Given the apparently different underlying pathophysiology of mental stress-induced ischemia compared with exercise-induced ischemia, it is clear that conceptual constructs that serve as a basis for diagnostic testing and treatment of patients with chronic CAD are not sufficient to address patients with vulnerability to mental stress-induced ischemia and the associated poorer prognosis. Pathophysiologic constructs need to be established, and associated diagnostic and treatment models need to be developed and tested, so that patients who are vulnerable to mental stress can be identified and can receive appropriate treatments. Clearly, new approaches are needed. Their development requires an understanding of the differences between the conditions associated with exercise (demand) and those associated with mental stress-induced ischemia (cognitive).

The stimulus for myocardial ischemia that results from mental stress is cognitive and thereby differs fundamentally from the physical stimuli that provoke demand-related ischemia. Hostility and anger, emotional concomitants of mental stress, are associated with an increase in levels of inflammatory markers,[20] and episodes of anger are associated with an increased risk of myocardial infarction.[7] Although negative reactivity to stress has been shown to increase the risk of a poor outcome, individuals have different thresholds for expressing negative emotions as a result of stress, so that the risk of an event may depend not only on the individual's cardiovascular substrate but on his or her coping mechanism as well. Given the cognitive and emotional constituents of mental stress, an examination of the neurobiology of this phenomenon, with an eye toward "downwind" effects on the cardiovascular system, is in order if we are to proceed to the day when prognostic testing for mental stress-induced ischemia becomes a routine part of clinical practice.

The neurobiology of mental stress

When stress occurs, the stimulus for ischemia is located in the brain.[2,11,21] CAD patients who exhibit myocardial ischemia in response to laboratory mental stress should exhibit activation in subcortical regions associated with visceral effectors, such as the frontolimbic structures, compared with those who do not become ischemic.

The evaluative component of a psychosocial stress or confrontation occurs in the frontal cortex—specifically in the medial prefrontal cortex, where there are functional interconnections between it and the limbic system. The limbic system has visceral effectors and functional interconnections between the hypothalamus and pituitary, initiating the adrenal stimulation of epinephrine, which returns to the locus coeruleus to potentiate norepinephrine production. These interconnections shape the function of the amygdala and the hippocampus, and are important in coping mechanisms.

A prevailing theory is that differentially less activation of the frontal to the limbic reaction results in an unbalanced output of visceral effectors from the limbic system, which augments catecholamine output and various physiologic outcomes such as parasympathetic withdrawal and potentiation of coronary vascular dysfunction that results in myocardial ischemia.

The hippocampus provides the context from which we evaluate situations (eg, distinguishing a bear in the woods from a bear in the zoo). Patients with posttraumatic stress disorder have dendrite atrophy in the hippocampus, impairing their ability to accurately put into context their retrieval of long-term traumatic memories.

The amygdala has visceral effectors that shape the response to fear. The interaction between the amygdala and the limbic system may determine the appropriateness and the output of visceral neurosectors and the subsequent effect upon the heart.

BRAIN ACTIVATION PATTERNS IN MENTAL STRESS

We conducted O_{15} PET studies of the brain to map brain activation in response to laboratory stress (mathematical calculation) in subjects with or without CAD.[11] Echocardiography was also performed during the O_{15} PET imaging, enabling us to map patterns of brain activation in CAD subjects who experienced myocardial ischemia during stress and compare these patterns to those of the CAD subjects who did not exhibit myocardial ischemia during stress.

Different activation patterns in subjects with vs without CAD

Compared with otherwise healthy controls, subjects with CAD exhibited significantly increased blood flow in the left anterior cingulate, the left parietal cortex, and the left parahippocampus, areas that are involved in emotion, memory, and attention. In these CAD subjects there was greater limbic to prefrontal activity. This pattern of activation implies that the

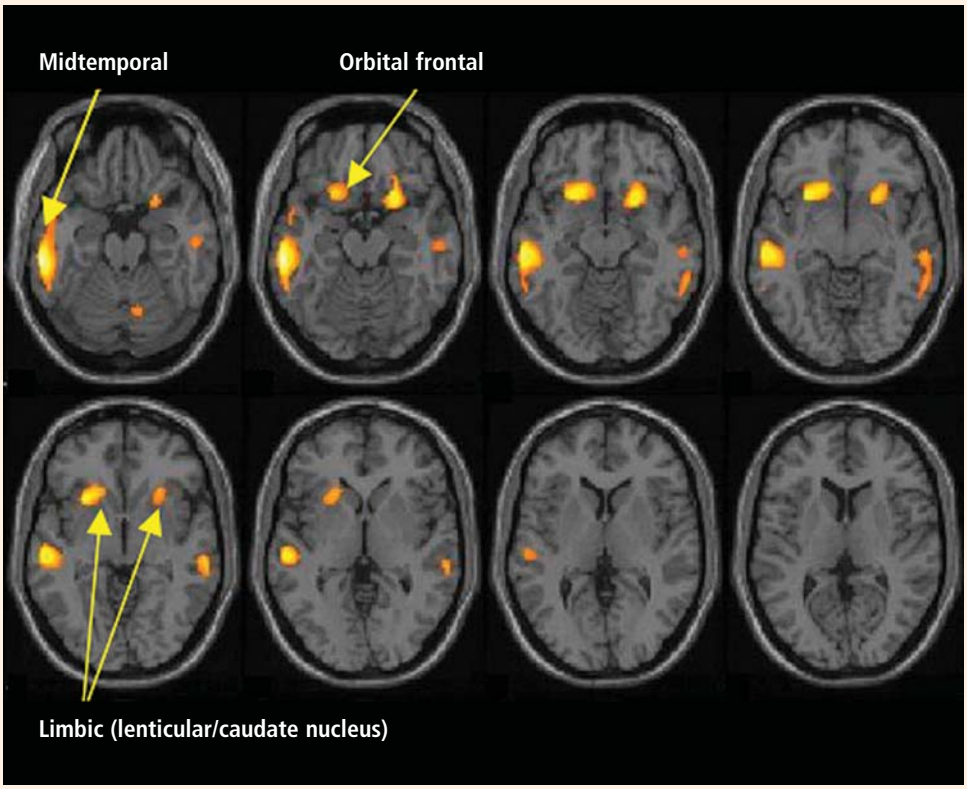

FIGURE 1. Subtraction scans showing areas of cortical activity in association with mental stress ischemia vs ischemia provoked by dobutamine. Activation is observed in the midtemporal, orbital frontal, and limbic lobes, the anterior cingulate gyrus, and the amygdala/hypothalamus (all $P < .01$), confirming that mental stress-induced ischemia is associated with a distinct pattern of central nervous system activation compared with demand-provoked ischemia. These areas are referable to the cognitive nature of mental stress and are associated with memory/emotion and sympathetic activation.

hyperactivation of limbic regions associated with fear and anxiety has a greater effect on cardiovascular function via effectors, which regulate neurohormonal responses and autonomic balance. Healthy subjects did not significantly exhibit these activations but instead exhibited activations that were referable to the cognitive effect of the task.

Thus, CAD subjects with ischemia had marked activation in the hippocampus and the anterior cingulate gyrus, both of which are involved in emotional processing and the processing of neurohormonal effectors. The subjects who developed ischemia had marked deactivation throughout their nondominant hemisphere, which suggests that the coping mechanism in response to stress that exists in the nondominant hemisphere is deactivated in subjects who exhibit ischemia.

Furthermore, during mental stress, CAD subjects also have specific activation patterns distinct from those in subjects without ischemia. These findings suggest pathways that may account for the silent nature of mental stress-induced ischemia, namely deactivation in the cingulate anterior gyrus.[22] The latter has been associated with varying thresholds for pain sensations.

Different activation patterns in men vs women

We next examined patterns of brain activation during mental stress in men and women with CAD and men and women without CAD.[23] We found no difference in patterns of brain activity between men and women without CAD during laboratory stress. Both had activation of the visual association cortex and other areas referable to numerically based tasks. The women with CAD, when compared to their counterparts without CAD, had greater activation in areas associated with neocortical and subcortical limbic structures. Of note, activation occurred in the prefrontal cortex (middle frontal gyrus and inferior frontal gyrus) in the women with CAD, which suggests an evaluative component to their central nervous system response to mental stress.

Women with CAD also had greater bilateral and medial temporal activation during mental stress (amygdala/hippocampus) when compared to men with CAD. Interestingly, men with CAD had deactivation in the same areas that were significantly activated in women with CAD during stress: the anterior cingulate, orbital frontal, and medial temporal anterior regions. Brain activation in women with CAD was also mainly bilateral, whereas it was more medial in men with CAD.

Different activation patterns as a function of ischemia during mental stress

We hypothesized that patients with mental stress-induced ischemia would show increased activation in brain regions that involve memory and emotion relative to subjects without mental stress-induced ischemia. We further hypothesized that this pattern of activation would differ from that seen in demand-related ischemia.

To test these hypotheses, we studied 58 patients

with CAD who underwent simultaneous measurement of brain activation with O_{15} PET and cardiac wall motion analysis (to evaluate myocardial ischemia) with echocardiography during arithmetic mental stress and dobutamine stress conditions.[24] Eight of the 58 subjects had ischemia to both mental stress and dobutamine stress. Thirteen had myocardial ischemia to mental stress but not in response to dobutamine stress.

When brain PET images were analyzed, cerebral hyperactivation was observed in the subcortical limbic and neocortical regions of the brain during mental stress relative to dobutamine stress. Again, activation was observed in frontolimbic circuits associated with emotion, memory, fear, and anxiety, which are areas also involved in neurohormonal and autonomic regulation. These findings suggest that ischemia to mental stress has a distinct cerebral activation pattern compared with ischemia that results from demand stimulus. Activated areas with ischemia that results from mental stress are referable to the cognitive nature of mental stress, and activation occurs in regions associated with memory, emotion, and sympathetic activation **(Figure 1)**.

SUMMARY

Mental and emotional stress can provoke transient ischemia and acute coronary syndrome in vulnerable patients. Furthermore, those patients so provoked are at increased risk for recurrent cardiac events and early death. Viable psychological treatments to improve prognosis exist, and preliminary trials demonstrate their efficacy with regard to short- and long-term outcomes, as well as economic savings.

These findings heighten the need for efforts directed toward the complete identification of the differential pathophysiology of mental stress-induced ischemia, with an eye toward development of diagnostic tests and establishment of risk stratification algorithms that can be applied in the clinical setting. Ongoing research in this vein is identifying unique aspects of the brain-heart relationship during mental stress that underlie the cognitive and emotional aspects of mental stress, and the "downwind" pathways by which distinct patterns of brain activity during mental stress can provoke otherwise silent myocardial ischemia. This research is making important contributions to the larger clinical goals associated with diagnostic testing, risk stratification, and treatment of patients at risk for mental stress-induced ischemia and poorer prognosis.

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