Neurocardiac Interaction During Stress-Induced Myocardial Ischemia
How Does the Brain Cope?

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“My life is in the hands of any rascal who chooses to put me in a passion.”

—Sir John Hunter

This quote from one of the major medical figures of the 18th century describes the association of his expression of anger to his experience of angina. In 1793, Dr Hunter was engaged in rancorous argument during the course of a faculty meeting and died suddenly. Narrative reports of angina pectoris in association with an individual’s experience of provocative, stressful circumstances, although not as dramatic as that made by Hunter, date from the time of Celsus to the dawn of modern medicine. These observations gave rise to the pioneering work of Rosenman et al on what they came to call “behavior pattern A.” Their work in turn encouraged others to pursue constitutional factors—the personality—that might give rise to risk for stress-related effects on the heart. The resulting literature on emotion, personality, and coronary artery disease (CAD) has, however, very often dealt with narrow concerns, without sufficient integration of biological and social variables that reflect the contextual nature of psychosocial stress. In addition, methodological drift in the conduct of studies on Type A and associated personality factors, combined with the failure in studies to account for concurrent progress in the care of the cardiac patient, produced results that conflicted with the earlier, promising findings. These issues have been discussed elsewhere. Hence, although we intuitively continue to link emotional factors and coronary syndromes, the nature of the link remains unclear.

One consequence of the conflicting research findings on stress, emotion, and coronary syndromes is the absence of a conceptual framework, which is necessary if an effect on clinical awareness and practice is to be realized. In our pursuit of this framework, few discriminators are available to guide our interpretations of the conflicting results of what had been promising lines of research. What is apparent is that the employment of personality traits as stable intrapersonal variables in the service of predicting long-term outcomes differs from an examination of episodic expressions of emotion or experiences of acute catastrophe as triggers of acute cardiac events. These approaches address different questions. One question asks if there are specific personality traits that promote and progress CAD over time. The other question asks if episodes of negative emotional reactions result in cardiac events in people with established CAD or a high likelihood for CAD. In the research domain, the expression of negative emotions in response to a real or perceived provocation seems to correlate consistently with acute cardiac events. In addition, mental stress administered acutely in a laboratory setting provokes myocardial ischemia in up to 40% of subjects with known CAD, and CAD patients who demonstrate wall motion abnormalities during this laboratory-administered mental stress appear to have a significantly heightened risk of cardiac events, including death, up to 5 years after this “mental stress” testing. It may be reasonable to assume that people with a clustering of negative personality traits are at increased risk of emitting negative emotional responses, thereby increasing their risk for cardiac events. However, the presence or absence of a specific cluster of personality traits as a predictor of CAD diverts our attention from the empirical association of episodes of emotional reactivity of sufficient physiological arousal to trigger these events.

Emotion is not a result of conceptual constructs of personality but rather of the brain’s reception of our visceral response to events in our lives and communities. Fear and anger may be emotions integral to certain personality traits such as hostility, and stress may be the context that provides the setting for negative emotions to manifest. These emotions also occur, albeit with less frequency, in people without predisposing traits, given sufficient environmental provocation. Hence, when we distinguish between personality traits that are assumed both to be stable over time and to predict CAD and episodes of angry/hostile responses that culminate in a clinical event, we begin to disentangle the research findings. Furthermore, if we focus on emotions as triggers for acute events, subsequent empirical inquiry—supported by studies in laboratory and naturalistic settings—may provide key observations that enable a conceptual construct of the contribution made by emotion to CAD. This then will provide the setting for the establishment of new paradigms necessary to guide clinical practice. The development of state-of-the-art imaging allows us to pursue these paradigms.

What Is Stress?
Stress may best be viewed as an interaction between the individual and his or her environment, shaped by past and
unfolding evolutionary determinants. During psychosocial confrontation, central cognitive processes incorporate stored memory to evaluate the circumstances, and, in concert with psychosocial and cultural influences, inform us as to which aspects of the circumstances are important. These processes also inform the nature of or necessity for a given response. Our learned memory includes essential emotional components that add motivational elements to the circumstances, thereby facilitating definition and significance of associated goals. A certain level of stress-related emotional and physiological activation is a useful accompaniment to the appraisal process, enhancing our performance and enabling us to obtain our goals. When, however, our history-based appraisal of a situation is inaccurate, the emotional and physiological activation are excessive, and the associated responses extend beyond what the circumstances require. The excessive response impairs our ability to further appraise our surroundings in a precise manner. If these processes are chronically employed, we react to daily hassles such as traffic delays and waiting on line as we would to real survival threats or important impediments to critical goals, which eventually results in a disruption to our physiological homeostasis. An observed biological relationship between our emotional responses and CAD outcomes would broaden our appreciation of the context in which heart disease unfolds. It follows that brain activation should be explored for the biological signals/patterns that may inform those processes that transduce emotion/cognition to cardiovascular end points.

The Neurocardiac Interaction in Mental Stress

**Stress, Learning, and Memory**

Recent research has guided our understanding into brain circuitry associated with stress and the emotions of fear and anger. Memory is retrieved from a complex network of associated cortical regions, a process that results in bodily sensations and shapes the biological coping response. In a susceptible individual, a recurrent response may result in long-term biological alterations in the brain and cardiovascular system. Differences in the formation, consolidation, and retrieval of long-term memory are relevant to an individual’s vulnerability to the cardiovascular manifestations of emotional stress.

The inappropriate mobilization of our stress/fear response may be explained in part by the classical conditioning paradigms explored by Pavlov in the early 1900s. This form of conditioning occurs when a reflexive physiological reaction to a particular (unconditioned) stimulus comes to be elicited by an irrelevant but initially paired (conditioned) stimulus. Hence, an inappropriate or irrelevant trigger replaces the initial eliciting trigger. With regard to the present discussion, when our stress/fear appraisal processes come to be paired with an irrelevant or inappropriate (from a survival or success standpoint) stimulus, our responses in the form of emotion and action may be out of proportion to circumstances. Thus, the brain in this manner reflexively initiates the stress/fear response to an inappropriate or irrelevant stimulus. The physiological underpinning by which the brain makes these associations is described by the overarching concept of brain plasticity. Neuronal associations are affected on a molecular level by the process of long-term potentiation observed in the hippocampus by the activation of the amino acid glutamate binding to specific NMDA receptors. Review and integration of this and associated processes of long-term potentiation are beyond the goal of this editorial.10

**Physiological Pathways: Stress Effector Systems**

Various stress effector systems serve as neural conduits that integrate cognitive cues and mediate the stress response. These stress effector systems include the sympathoneural system; the adrenomedullary hormonal system; the parasympathetic nervous system; and the hypothalamic–pituitary–adrenal axis, renin–angiotensin–aldosterone, and vasopressin systems.11 Sympathetic hyperactivation in response to both mental challenge and affective distress increases circulating levels of epinephrine and norepinephrine.4,12 The augmentation of the sympathetic nervous system activity causes neurohormonal release and subsequent diverse effects on hemodynamic activity and vasomotor tone. Further effects are seen with regard to platelet activation, endothelial injury, and arrhythmogenicity.13 The increased incidence of coronary events in the morning hours, when levels of these neurohormones are elevated as part of the amplitude of our circadian biovariability, is one naturalistic example of these effects. It is interesting to note that in many natural catastrophes an increase in cardiovascular events was reported to occur during the early morning hours.14 The San Francisco earthquake of 1989, which occurred in the late afternoon, was not associated with an increase in these cardiovascular episodes.9

The precise interplay of various mechanisms in the regulation of coronary flow during mental stress is not fully understood. It is noteworthy that subjects who become ischemic to both exercise and mental stress may display similar rate-pressure products during these provocations.15 However, this product is achieved by more of a contribution from heart rate in exercise stress and from blood pressure in mental stress. Accordingly, despite an increase myocardial demand in both triggers of ischemia, the systemic vascular resistance increases in response to mental stress and declines in response to exercise stress. The interaction between α-adrenergic–mediated flow and resistance may therefore be an important determinant in the observed decrement in absolute myocardial blood flow and in plaque disruption in the presence of minimal epicardial stenosis in mental stress ischemia.16,17 In addition, β-adrenergic receptors are stimulated during stress as a result of catecholamine release. This leads to an increase in contractility and heart rate, and overall, the myocardial oxygen demand increases during mental stress in a manner similar to exercise. Coincident with this heightened sympathetic response to stress, a decrement in vagal tone has been consistently noted by several studies. Vagal withdrawal during stress accentuates autonomic balance toward receptor-mediated effects on myocardial flow, contractility, hemodynamic resistance, and arrhythmic threshold.14

**Brain Map of Stress**

Methods such as positron emission tomography and functional magnetic resonance imaging possess the unique ability to create functional images of the brain. Given that the stimulus for ischemia with mental stress initiates in the brain,
it makes sense that we would turn our attention to the central nervous system to observe activations that may account for this heightened neurohormonal response. Neuroscientists have described the biology of emotion in unparalleled detail in recent years. The neural circuits of emotion have become as tangible as those of auditory and visual processes. The components of the emotional circuits interact functionally and include the prefrontal lobes, limbic system, and those portions of the cortex that are functionally connected and activated as determined by the stimulus (eg, the somatosensory cortex in response to intestinal peristalsis/pain or motor to “flight”). Our response (eg, fear, anger, sadness) to stressful cues is influenced by the manner and degree to which we process these cues in specific cortical regions. In general, environmental cues that are processed more by limbic structures and less by the prefrontal cortex are associated with greater physiological reactivity. The components of the limbic system are the hypothalamus, which controls various biological functions; the hippocampal complex, which provides memories and context; the amygdala, which integrates information from other brain regions; and the cingulate gyrus, which helps form connections that create our awareness of emotions. These structures in the limbic system interact and provide the perception of danger, our experience of fear (amygdala), and the assignment of meaning to our perceptions, as well as contextual information (hippocampus).

These regions form a network for evaluation of environmental stimuli, initiating a process that results in visceral sensations, such as palpitations and diaphoresis, that are integral to our experience of emotion. When we experience stress, an initial evaluative process in the central nervous system shapes our response. This cognitive evaluation occurs in the prefrontal/frontal cortices. The lateral prefrontal cortex has connections to auditory, visual, and motor regions, as well as other areas associated with emotion and memory (hippocampus, cingulate, amygdala, and temporal regions). In this manner, our brain’s response to stress integrates evaluative, auditory, visual, and motor responses. Relevant to the biological consequences of the cardiovascular neurohormonal response to stress, the quality of cognitive evaluation in the prefrontal/frontal cortices serves to shape the manner in and degree to which we retrieve memories. The latter is influenced by the conditioned responses that have occurred and are ongoing in accord with the concepts of brain plasticity. Often we respond to new situations on the basis of previous experiences that are stored as memories. Memories are divided according to qualitative and temporal attributes. “Explicit or declarative” memories are associated with the hippocampus, and “implicit/unconscious” memories are associated with the amygdala. The hippocampus and amygdala interact in extracting long-term memory in various emotional contexts that condition our behavioral responses to stress and fear.

The cardiovascular effects of stress are executed through the brain’s neurochemical pathways associated with fear and anxiety. Several regional central nervous system centers are neuroanatomically and functionally interconnected to form a network that initiates and shapes sympathoadrenal responses. Initiation occurs in the prefrontal/frontal cortices and subcortical (limbic) structures. Below the cortex are several neuronal networks in the brainstem, one of which is the solitary tract. These neuronal centers send afferent signals to the locus ceruleus, the major source of norepinephrine-producing neurons, which reamplifies the cortical process via projection to the hypothalamus. In addition, the hypothalamus (the brain’s major corticotropin-releasing hormone–producing region) projects to limbic and frontal regions, integrating memory, learning, and evaluation of internal and external cues that modulate the frequency and magnitude of hypothalamic discharge. The hypothalamus, therefore, is influenced not only by lower (brainstem) but also by higher frontal cortical regions related to evaluation and by subcortical limbic areas related to memories that are explicit (hippocampus) and implicit (amygdala). In this manner, the brain and the biological reactions are integrated and produce the stress response.

When CAD subjects are compared with healthy controls, highly significant activations occur in limbic structures associated with emotion and memory during laboratory mental stress, similar to the brain maps of fear found in people with posttraumatic stress disorder. CAD subjects who become ischemic in response to mental stress show hyperactivation in the hippocampus and deactivation in the anterior cingulate (a pain center) compared with CAD subjects without ischemia. These activations may influence the pathophysiology and clinical presentation of mental stress ischemia (MSI). More work is underway to establish the specific cerebral correlates of vagal withdrawal and the silent nature of MSI. Emerging and extant literature suggests that MSI has pathophysiological distinctions in cerebral and cardiovascular determinants compared with exercise; poor prognosis; and survival advantage when rehabilitation strategies are tailored accordingly. Although we use exercise as a stimulus for ischemia, many patients who experience ischemia at rest do not experience ischemia during exercise. Furthermore, strong emotions are demonstrated triggers of acute coronary syndrome. The standardization and implementation of clinical mental stress testing may be an important adjunct in the diagnosis of individuals vulnerable to MSI.

Behavior is shaped by latent and manifest social determinants that inform cultural expectations and attitudes. An individual’s biological substrate interacts in this context through genetic, endocrine, immune, and neural processes. Funding for initiatives that integrate social, behavioral, and biomedical contributions to stress and cardiac disease is afoot. In the past several decades, cardiology has grown into social and molecular scientific domains. How attitudes shape our health in a social context requires integration and expansion of this growth. Serious inquiries about stress and the heart are incomplete without expansion into that which transduces much of the physiological response—the brain.

References


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