Acute Psychological Stress as a Precipitant of Acute Coronary Syndromes in Patients With Undiagnosed Ischemic Heart Disease: A Case Report and Literature Review

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Objectives: Acute psychological stress causes a number of physiologic responses that can trigger acute coronary syndromes in individuals with silent coronary artery disease. The mechanisms behind this phenomena have been the subject of much speculation. The following is a case report and brief review of the literature.

Method: A PubMed search was undertaken using the key words *stress and myocardial infarction, stress and ischemia, mental stress and coronary artery disease, psychological stress and acute coronary syndrome*, and *mental stress and plaque destabilization*. Articles were restricted to the English language and those dating through December 2007.

Results: Acute coronary syndrome is thought to be the end result of a complex mechanism involving platelet activation and endothelial dysfunction. Several studies have shown that acute mental stress leads to enhanced platelet activation and endothelial dysfunction. The mechanism behind this involves both the autonomic nervous system and the neuroendocrine response.

Conclusions: Acute psychological stress may lead to acute coronary syndromes in patients with previously silent disease. Physicians should inquire about cardiac symptoms in patients with cardiac risk factors who are experiencing psychological distress. Further research will hopefully lead to an improved understanding of the mechanism behind this process to improve therapeutic interventions.

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Acute coronary syndromes (ACSs) are the result of plaque disruption stemming from a complex interplay between hemodynamic factors, inflammatory modulators, and endothelial dysfunction. The subsequent platelet activation and thrombus formation results in the downstream ischemia and possible infarction of coronary tissue. The relationship between ACS and acute mental stress has been well documented.[1–3] However, the precise mechanism by which acute mental stress leads to plaque destabilization and thrombus formation has yet to be elicited. A growing body of literature suggests several abnormalities in platelet activation and endothelial function during acute mental stress that could precipitate ACS in patients with silent coronary artery disease. The following is a case report of a patient with silent ischemic heart disease that was unmasked in the setting of acute psychological stress. Following the case report is a brief discussion about the pathophysiology linking mental stress and acute coronary events.

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CASE REPORT

A 50-year-old male with no past medical history presented to the emergency room (ER) at the urging of family 2 days after the death of his wife with a 1 hour and 45-minute history of bilateral arm pain, diaphoresis, and a feeling of tightness in his throat. The episode began while he was sitting with his in-laws discussing plans for his wife's funeral, which was to be the following day. He stated he began sweating profusely and then noted a pressure sensation in his shoulders that soon descended to the elbows accompanied by a tightness in his throat. He denied having any nausea, shortness of breath, or chest pain.

The patient had several coronary risk factors, including a 14 pack-year smoking history and significant alcohol

intake ranging from 5–10 beers per day on average. On days when he did not drink, he denied any symptoms of withdrawal. He described himself as a very active person, working as a carpenter. The 19 months prior to his presentation had been particularly stressful, as his wife was battling colon cancer. The last 2–3 months of her life were spent in home hospice care where the patient was the primary caregiver helping with medications, feeding, and other activities of daily living. Several months prior to presentation, the patient had an episode of chest pain while driving that lasted several minutes. At the time he dismissed this as "a normal reaction to stress." During his wife's illness, the patient stated there were times when he felt depressed, which he defined as a feeling of sadness. He denied difficulty concentrating, fatigue, anhedonia, irritability, anorexia, insomnia, hypersomnia, hyperphagia, or suicidal ideations. After her death, the patient denied any elements of psychosis and his clinical picture was most consistent with normal bereavement.

In the ER, serum creatine kinase myocardial band level was 39 ng/mL, creatine kinase index was 16.4 IU/L, and troponin level was 1.87 ng/mL. Electrocardiogram showed elevated ST segment in leads II, III, and aVF. He was diagnosed with an inferior myocardial infarction and underwent stenting during catheterization. He was discharged the next day to attend his wife's funeral.

PATHOPHYSIOLOGY OF ACUTE CORONARY EVENTS

Acute coronary syndrome is a complex interplay between multiple factors that ultimately result in atherosclerotic plaque destabilization, rupture, and subsequent thrombosis. Endothelial dysfunction and platelet activation are thought to be critical in the transition from asymptomatic disease to a possibly life threatening myocardial event.

The endothelium has a number of functions, including regulation of inflammation, vascular tone, and coagulation.[4,5] Endothelial dysfunction can result from trauma, infection, hypertension, diabetes, smoking, or low-density lipoprotein deposition and subsequent oxidation in the vessel wall.[5] The resulting reduction of nitric oxide production and other endothelial-derived factors results in vasoconstriction, increased expression of cellular adhesion molecules, inflammatory cell recruitment, decreased expression of tissue plasminogen activator, increased production of plasminogen activator inhibitor, increased secretion of von Willebrand factor (vWF), collagen exposure, increased thrombin production, and platelet activation.[4–6] These factors combine to create a microenvironment of chronic inflammation and a procoagulant state. The combination of chronic inflammation and shear stress promote rupture of vulnerable atherosclerotic plaques.

The ruptured plaque triggers an inflammatory response that accentuates platelet activation through the production of various cytokines and oxygen free radicals. Platelet membranes contain receptors for several different agonists capable of inducing and perpetuating platelet activation. Thromboxane A2, adenosine diphosphate, and thrombin are all potent platelet activators whose production is increased during inflammatory states.[6] All 3 act at G-protein coupled receptors to increase intracellular calcium and decrease intracellular cyclic adenosine monophosphate. The net result is a change in the ligand-binding properties of the glycoprotein IIb/IIIa receptor rendering it capable of binding vWF and fibrinogen.[4] The conformational change in the IIb/IIIa receptor is thought to be the common final pathway by which platelet aggregation and subsequent thrombosis occur.

PSYCHOLOGICAL STRESS AND ENDOTHELIAL DYSFUNCTION

The role of endothelial dysfunction in the pathogenesis of ACS has been well documented.[4,5,7–9] Acute mental stress has also been associated with endothelial dysfunction.[10–12] Ghiadoni et al.[11] found reduced brachial artery flow–mediated dilation in healthy subjects following exposure to mental stress. Spieker et al.[12] found similar results. However, infusion of an endothelin-A receptor antagonist prevented impairment of flow-mediated dilation in the latter study. This suggests that impaired vasodilation may be mediated through this receptor. An increase in endothelin-1 has been observed following administration of corticotropin-releasing hormone (CRH), which is known to be elevated during psychological stress.[13,14] Hyperactivity of the hypothalamic-pituitary-adrenal axis resulting in elevated CRH and overstimulation of the endothelin-A receptor is one possible mechanism for the observed endothelial dysfunction. Additionally, in a study of 31 healthy volunteers, Eriksson et al.[15] found that impairment of endothelial vasodilation in the setting of acute stress could be attenuated by propranolol but not phentolamine, suggesting a role for β adrenergic receptors.

Similar to that observed in healthy controls, patients with established coronary artery disease (CAD) demonstrate similar impairments in flow-mediated dilation as well as paradoxical constriction.[16–18] Consequently, patients with CAD may be at increased risk for myocardial ischemia in the setting of acute stress relative to healthy controls.

PSYCHOLOGICAL STRESS AND PLATELET ACTIVATION IN PATIENTS WITH CAD VS. HEALTHY CONTROLS

Platelet activation leads to aggregation, degranulation, protein secretion, and ultimately thrombus formation. Nu-

merous studies have suggested abnormalities in platelet activation during acute mental stress.[19–27] Several methods have been used to measure activation, including serum levels of secretory products such as adenosine triphosphate, platelet factor 4, thromboxane A2, and β-thromboglobulin. More recently, flow cytometry has been used to measure platelet-leukocytes aggregates (PLAs) as an indicator of platelet aggregation. Several studies have reported increased levels of PLAs, ATP, plasma thromboxane A2, platelet factor 4, and β-thromboglobulin in healthy subjects upon exposure to mental stress, suggesting heightened platelet activation.[19–21,24–27]

Further abnormalities have been demonstrated in patients with coronary artery disease. In a comparison of 25 postinfarction patients to 10 healthy controls following exposure to emotional stress, Grignani et al.[25] found between-group differences in platelet aggregation products with the CAD patients showing significantly increased aggregates. Similarly, Wallen et al.[28] found that angina patients had shorter platelet aggregability times than healthy controls as well as increased levels of platelet factor 4 and β-thromboglobulin. Strike et al.[21] demonstrated similar increases in platelet-leukocyte aggregates after exposure to mental stress in men with and without CAD. However, PLA serum levels returned to baseline in patients without CAD, whereas they remained elevated 75 minutes after the stressful stimuli in patients without CAD. In summary, these studies suggest that heightened platelet activation may be a physiologic response to stress in healthy controls. However, this response may be exaggerated and slow to attenuate in patients with CAD predisposing them to ACS.

PSYCHOLOGICAL STRESS AND THE SYMPATHETIC RESPONSE

Although heightened platelet activation is well supported by the literature, the mechanism leading to this activation is unclear. Acute stress has also been associated with elevations in heart rate, blood pressure, and serum catecholamines.[19,20,23,25,26] Platelet activation may be part of the systemic sympathetic response and consequence of hemodynamic reactivity. Steptoe et al.[20] found that increases in platelet-leukocyte aggregates after exposure to psychological stress were associated with systolic blood pressure reactivity. Similarly, Patterson et al.[27] found platelet activation to be positively correlated with serum norepinephrine levels but not changes in heart rate or blood pressure. They found a negative correlation between platelet activation and serum epinephrine. Levine et al.[26] observed increases in platelet activation and serum catecholamines. However, neither propranolol nor phenoxybenzamine in doses known to block the β_1 and α_1 receptors modified platelet activation. Administration of propranolol resulted in significantly lower blood pressure and heart rate elevations than placebo. These results suggest that platelet activation and hemodynamic reactivity are modulated, at least in part, by different factors. It has been hypothesized that platelet activation in the setting of acute mental stress is a delicate balance between the stabilizing effects of β_2 receptors and destabilizing effects of α_2 receptors located on the plasma membrane.[26,27]

CONCLUSION

Acute mental stress causes increased platelet activation and endothelial dysfunction in healthy patients. These physiologic aberrations may be increased in CAD patients rendering them more susceptible to ACS in the setting of psychosocial stressors. Physicians should be aware that acute mental stress can precipitate coronary events in patients with a previously silent disease. Warning signs may be ignored by patients who are preoccupied or dismissed as "normal reactions to stress." Patients with known risk factors for CAD, including family history, diabetes, renal disease, smoking, and alcohol use, should be carefully questioned during stressful times for cardiac symptoms. Additionally, physicians caring for patients with such risk factors should routinely inquire about the presence of psychosocial stressors and social support. Future work will hopefully allow a better understanding of the mechanisms involved to aid in advancing therapeutic interventions.

Drug names: phenoxybenzamine (Dibenzyline), phentolamine (Oraverse, Regitine, and others), propranolol (Innopran, Inderal, and others).

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