Mental stress, a powerful provocateur of myocardial ischemia: Diagnostic, prognostic, and therapeutic implications

Diwakar Jain, MD, FACC, FRCP, FASNC

See related article on p. 518

Coronary artery disease (CAD) is a major health problem on a global scale. CAD afflicts an estimated 14 million patients in the United States, and 1 million patients have an acute cardiac event every year. CAD has a long protracted course spanning over decades, including variable periods of silent buildup of coronary plaques, symptoms of angina, and chronic disability from its long-term sequelae. The natural history of CAD is punctuated by acute catastrophic events of myocardial infarction, unstable angina, arrhythmias, and congestive heart failure. Each event takes a heavy toll in terms of death and disability. Hyperlipidemia, smoking, diabetes, hypertension, obesity, family history of premature CAD, and physical inactivity are widely recognized risk factors for CAD. Prevention and treatment of these risk factors have substantially reduced the rates of morbidity and mortality from CAD. Nevertheless, CAD continues to be the single most important cause of morbidity and death all over the world. The search for unidentified and less well-appreciated risk factors and pathogenic mechanisms is still on. The risk factors for buildup of atheromatous plaques are well appreciated, but the risk factors that punctuate the course of this long-drawn process with acute catastrophic episodes are not fully known.

Despite the identification of emotional stress as a trigger in the first description of angina pectoris by Heberden, as well as the well-publicized death of John Hunter, a renowned British surgeon, in 1793, after a heated argument with his colleagues, the role of mental stress and behavioral and psychological factors in cardiovascular medicine has remained inadequately understood.[1] Unlike hyperlipidemia, smoking, diabetes, and hypertension, psychological and behavioral factors do not readily lend themselves to scientific scrutiny in an objective, quantitative, controlled, and reproducible manner by use of the conventional research tools. In recent years a number of innovative studies have explored these areas and have shown an important interaction between behavioral and psychological variables and CAD. These studies also provide new and challenging opportunities for nontraditional therapeutic interventions in CAD.

From the Section of Cardiology, Nuclear Cardiovascular Imaging Laboratory, Drexel University College of Medicine, Philadelphia, Pa.
Reprint requests: Diwakar Jain, MD, FACC, FRCP, FASNC, Section of Cardiology, Nuclear Cardiovascular Imaging Laboratory, Drexel University College of Medicine, MS 470, 245 N 15th St, Philadelphia, PA 19102-1192; *Diwakar.Jain@Drexelmed.edu.*
J Nucl Cardiol 2008;15:491-3.
1071-3581/$34.00

doi:10.1016/j.nuclcard.2008.05.003

MENTAL STRESS AND MYOCARDIAL ISCHEMIA

Whereas increased physical activity and exercise are well known to result in myocardial ischemia in CAD, mental stress has only recently been recognized as a provocateur of myocardial ischemia. Laboratory models of mental stress result in left ventricular dysfunction, regional wall motion, and perfusion abnormalities in a significant proportion of patients with CAD.[2-11] Burg et al[2] observed a structured psychological interview and mental arithmetic, 2 commonly used mental stress tasks, to result in a significant decrease in left ventricular ejection fraction, a marker of myocardial ischemia, in nearly half of their patients with CAD. Reversible myocardial perfusion abnormalities similar to those induced by exercise have also been observed in a significant proportion of patients with CAD.[6-8] Whereas the intensity and level of physical exercise and the severity of CAD are the important determinants of exercise-induced myocardial ischemia, behavioral traits are the most important determinant of mental stress–induced myocardial ischemia.[2] Burg et al observed high levels of hostility, anger, and type A behavior to be predictive of mental stress–induced myocardial ischemia in CAD patients. The severity of disease on coronary angiography or the severity of myocardial ischemia on exercise perfusion imaging was not predictive of mental stress–induced myocardial ischemia. Allam et al[8] observed that in 90% of patients with exercise-induced myocardial ischemia, myocardial ischemia developed on mental stress testing. Mental stress–induced myocardial ischemia was generally smaller compared with exercise-induced myocardial ischemia. However, in a small pro-

portion of patients (20%), mental stress resulted in a greater ischemia compared with exercise.

Unlike exercise-induced myocardial ischemia, chest pain and electrocardiographic changes of ischemia are infrequent with mental stress–induced ischemia. The exact reason for this difference is not clear. This, however, necessitates the use of relatively sophisticated modalities such as myocardial perfusion imaging and left ventricular wall motion and ejection fraction analysis for studying mental stress–induced myocardial ischemia. These factors may also have contributed to mental stress not being widely recognized as a provocateur of myocardial ischemia.

Mental stress–induced left ventricular dysfunction in patients with CAD is associated with an increase in peripheral vascular resistance and decreases in cardiac output and stroke volume.[12] In contrast, a decrease in peripheral vascular resistance and increases in stroke volume and cardiac output with mental stress were observed in mental stress–negative patients and in healthy subjects. This indicates abnormal vasoreactivity in mental stress–positive patients, which in turn correlates with higher levels of anger, hostility, and type A behavior.

PROGNOSTIC VALUE OF MENTAL STRESS–INDUCED MYOCARDIAL ISCHEMIA

The prognostic value of exercise or pharmacologic stress testing is well established.[13] However, the prognostic value of mental stress–induced myocardial ischemia is inadequately defined. We observed CAD patients with mental stress–induced left ventricular dysfunction to have a 3-fold higher incidence of adverse cardiac events on follow-up compared with patients with no left ventricular dysfunction with mental stress.[14] The demographic variables and conventional indices of CAD severity were not predictive of adverse cardiac events in this patient population, and this prognostic value was independent of exercise-induced myocardial ischemia. The role of mental stress–induced left ventricular dysfunction as being a powerful predictor of subsequent adverse cardiac events has now been confirmed by several other independent, albeit smaller, studies.[15-17] The exact mechanism of this association is not known. Perhaps abnormal coronary vasoreactivity, which results in frequent unrecognized episodes of myocardial ischemia during the course of these patients' day-to-day lives and social interactions, predisposes them to catastrophic cardiac events.

The study by Hassan et al[18] in this issue of the *Journal* adds further to our understanding of mental stress–induced myocardial ischemia and its clinical implications. They performed single photon emission computed tomography myocardial perfusion imaging during stress (exercise or pharmacologic stress), during mental stress, and at rest in 187 patients with CAD. Ischemia developed with exercise or pharmacologic stress in 33% of these patients, and ischemia developed with mental stress in 19%. The investigators also found a number of very interesting findings: In general, the extent and severity of ischemia were greater with exercise or pharmacologic stress compared with mental stress. However, 11% of the patients showed ischemia with mental stress but no ischemia with exercise or pharmacologic stress. This indicates that the mechanisms of mental stress and exercise-induced stress may be quite distinct from each other. Exercise-induced ischemia is demand-induced ischemia, where luminal narrowing limits increases in myocardial blood flow in response to increased demand, whereas mental stress–induced myocardial ischemia appears to be related to abnormal coronary vasomotion and an abnormal constrictive response in response to mental stress. This may be reflective of a combination of underlying abnormalities in endothelial function, autonomic function, and perhaps composition of the underlying plaque. Mental stress–induced changes in regional myocardial perfusion and function may thus turn out to be an important tool in studying coronary physiology, vasoreactivity, and pathobiology and perhaps in explaining several missing links in this field. This is supported by a strong association of mental stress–induced abnormalities in left ventricular ejection fraction and perfusion with adverse cardiac events on follow-up. It is tempting to speculate that mental stress testing may fulfill our quest for identifying "vulnerable plaques" that are likely to result in adverse cardiac events in the near future. It also opens up a potential therapeutic window of opportunity in patients with CAD. Because mental stress–induced myocardial ischemia was found to occur in patients characterized by clinically identifiable behavioral attributes such as high levels of anger, hostility, and type A behavior, it is likely that cognitive behavior therapy directed toward lowering these toxic behavioral elements may result in an improved outcome in this patient population.

However, despite interesting and challenging data provided by Hassan et al[18] and several other investigators, mental stress testing and psychological evaluation have not become standard entities in routine clinical practice. This may be because of several factors.

A lack of a uniform and standardized protocol for mental stress testing in clinical studies has hindered research in this area. A number of different mental stress tasks, such as mental arithmetic, anger-recall or stress interview, and color Stroop test, have been used in different studies, and different investigators have used their own versions of these tests. There is a need for

standardization of a mental stress testing protocol that can be used by standard nuclear imaging laboratory personnel with appropriate training. Perhaps an anger-recall test for 6 to 8 minutes may be an effective, reproducible, and easy-to-use task for mental stress testing in the nuclear cardiology laboratory.[19] Despite a fairly large volume of extant literature on mental stress testing, there is still a need for much larger studies involving thousands of patients to establish the diagnostic, prognostic, and therapeutic implications of data obtained from mental stress testing and its comparison to standard exercise or pharmacologic stress testing before mental stress testing can become an integral part of the routine evaluation of patients with known or suspected CAD. Perhaps nuclear cardiology, with its roots firmly grounded in the sound principles drawn from the disciplines of physiology, biochemistry, molecular and cell biology, pathology, and medical innovation should take a lead in studying mental stress and eventually incorporating it in its folds.

Acknowledgment

The author has indicated he has no financial conflicts of interest.

References

1. McGrew RE. Encyclopedia of medical history. New York: McGraw-Hill; 1985.
2. Burg MM, Jain D, Soufer R, Kerns RD, Zaret BL. Role of behavioral and psychological factors in mental stress-induced silent left ventricular dysfunction on coronary artery disease. J Am Coll Cardiol 1993;22:440-8.
3. Rozanski A, Bairey CN, Krantz DS, Friedman J, Resser KJ, Morell M, et al. Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. N Engl J Med 1988;318:1005-12.
4. Ironson G, Taylor CB, Boltwood M, Bartzokis T, Dennis C, Chesney M, et al. Effects of anger on left ventricular ejection fraction in coronary artery disease. Am J Cardiol 1992;70:281-5.
5. Goldberg AD, Becker LC, Bonsall R, Cohen JD, Ketterer MW, Kaufman PG, et al. Ischemic, hemodynamic, and neurohormonal response to mental stress and exercise stress: Experience from the psychophysiological investigations of myocardial ischemia study (PIMI). Circulation 1996;94:2402-9.
6. Deanfield JE, Shea M, Kensett M, Horlock P, Wilson RA, de Landsheere CM, et al. Silent myocardial ischaemia due to mental stress. Lancet 1984;2:1001-5.
7. Giubbini R, Galli M, Campini R, Bosimini E, Bencivelli W, Tavazzi L. Effects of mental stress on myocardial perfusion in patients with ischemic heart disease. Circulation 1991;83(Suppl): II100-7.
8. Allam A, Abbas F, Meneisy T, et al. Relationship between mental stress and exercise induced perfusion abnormalities in coronary artery disease [abstract]. Circulation 1999;100(Suppl):I-377.
9. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192-217.
10. Carpeggiani C, Skinner JE. Coronary flow and mental stress. Experimental findings. Circulation 1991;83(Suppl):II90-3.
11. Soufer R, Bremner JD, Arrighi JA, Cohen I, Zaret BL, Burg MM, et al. Cerebral cortical hyperactivation in response to mental stress in patients with coronary artery disease. Proc Natl Acad Sci U S A 1998;95:6454-9.
12. Jain D, Shaker SM, Burg MM, Wackers FJTh, Soufer RS, Zaret BL. Effects of mental stress on left ventricular and peripheral vascular performance in patients with coronary artery disease. J Am Coll Cardiol 1998;31:1314-22.
13. Jain D. ^{99m}Technetium labeled myocardial perfusion imaging agents. Semin Nucl Med 1999;29:221-36.
14. Jain D, Burg M, Soufer R, Zaret BL. Prognostic implications of mental-stress induced silent left ventricular dysfunction in patients with stable angina pectoris. Am J Cardiol 1995;76:31-5.
15. Jiang W, Babyak M, Krantz DS, Waugh RA, Coleman RE, Hanson MM, et al. Mental stress-induced myocardial ischemia and cardiac events. JAMA 1996;275:1651-6.
16. Krantz DS, Santiago HT, Kop WJ, Bairey-Merz CN, Rozanski A, Gottdiener JS. Prognostic value of mental stress testing in coronary artery disease. Am J Cardiol 1999;84:1292-7.
17. Sheps DS, McMahon RP, Becker L, Carney RM, Freedland KE, Cohen JD, et al. Mental stress-induced ischemia and all-cause mortality in patients with coronary artery disease: Results from the Psychophysiological Investigations of Myocardial Ischemia study. Circulation 2002;105:1780-4.
18. Hassan M, York KM, Li Q, Lucey DG, Fillingim RB, Sheps DS. Variability of myocardial ischemia responses to mental stress versus exercise or adenosine stress in patients with coronary artery disease. J Nucl Cardiol 2008;15:518-25.
19. Jain D, Joska T, Lee FA, Burg MM, Lampert R, Zaret BL. Day-to-day reproducibility of mental stress-induced left ventricular dysfunction in patients with coronary artery disease and its relationship to autonomic activation. J Nucl Cardiol 2001;8:347-55.