Mental Stress–Induced Ischemia and All-Cause Mortality in Patients With Coronary Artery Disease

To the Editor:

Recently, an article in Circulation discussed the prognostic utility of mental stress–induced wall motion abnormalities. The conclusion reached in the article is that the association between wall motion abnormalities during mental stress and mortality is important and probably underestimated by the unadjusted risk ratio of 2.79 (1.00 to 7.85). The authors suggest that investigations should be undertaken to determine whether a cheaper version of this test could be developed for the clinical setting.

Before drawing such conclusions, alternative explanations of the findings need exploration. There were 17 deaths in this study. Wall motion abnormalities during the speech test were observed among 37 patients. A total of 6 patients were observed to have wall motion abnormalities during the speech test and then die within the follow-up period. Because the results of the paper were based on so few events, controlling for multiple potential confounders simultaneously was not possible but was probably desirable.

Moreover, wall motion abnormalities during the speech test did not appear to have been chosen a priori to represent mental stress–induced ischemia. During both the Stroop and speech stress tests, several measures of mental stress–induced ischemia were evaluated, including ST-segment depression and reduced ejection fraction, as well as wall motion abnormalities. Indeed, numerous other measures of response to mental stress, such as blood pressure, heart rate, and catecholamine response, were reported, and these were not associated with mortality. Only wall motion abnormalities during the speech test were found to be associated with mortality. Multiple comparisons could account for the marginally significant result for wall motion abnormalities, and the lack of consistency across stress response measures does not inspire confidence in the reported association.

The possibility of a relationship between mental stress and cardiovascular mortality is an intriguing one. This article represents a thought-provoking exploratory analysis, and yet its conclusions are strong and unqualified. I would like to propose that wall motion abnormality provoked by a public speaking task was the single most sensitive indicator of myocardial ischemia.

Before performing the follow-up reported in our article, we had shown that ST segment depression was much less sensitive an indicator of mental stress ischemia than radionuclide measures. We and others had also shown that decreased ejection fraction in response to mental stress in many cases does indicate ischemia, but that a substantial proportion of normals also have ejection fraction decreases, probably as a reflection of increased afterload rather than ischemia. Because ejection fraction decrease does not appear to be a highly specific marker of ischemia in response to mental stress, it is not surprising that the PIMI data did not associate ejection fraction changes with increased mortality risk. Changes in blood pressure, heart rate, and catecholamines occur with mental stress, but do not differentiate people with myocardial ischemia from those without. Rather than weakening our case, the fact that these other responses do not predict mortality supports a specific, mechanistic link between mental stress ischemia and mortality.

Previous investigators have shown an adverse prognosis associated with mental stress–induced ischemia. Therefore, our findings are consistent. The reason we were able to show an increase in mortality associated with mental stress ischemia is that we studied a larger number of patients and followed them for a longer period of time. Because of the relatively small number of deaths in our study, we concur that additional prospective studies are needed where patients are followed-up not only for mortality, but for other cardiovascular events as well.

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Response

Dr. Schellenbaum and colleagues suggest that our finding of a relationship between mental stress–induced ischemia and subsequent cardiovascular mortality may be spurious. They point to the relatively small number of deaths and a “lack of consistency” between different mental stress variables and future mortality.

In fact, the Psychophysiological Investigations of Myocardial Ischemia (PIMI) study was a carefully designed multicenter study with several prespecified a priori hypotheses. Radionuclide measures of myocardial ischemia (wall motion abnormality and change in ejection fraction) were prespecified as the most important variables to be analyzed as indicative of myocardial ischemia. Our baseline studies in this population demonstrated that wall motion abnormality provoked by a public speaking task was the single most sensitive indicator of myocardial ischemia.

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