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EDITORIAL COMMENT

Mental Stress, Exercise, and Other Determinants of Elevation in High-Sensitivity Troponin Levels

A Call for Standardization of Laboratory Protocols*

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Cardiac troponins serve as sensitive markers of cardiomyocyte necrosis that facilitate the diagnosis of acute coronary syndromes. In recent years, there has been increasing interest into the clinical value of assessing high-sensitivity cardiac troponin (hs-cTn) T and I (hs-cTnI) assays that can detect 10-fold lower concentrations of troponin than conventional assays. Of note, elevations of troponin levels by a high-sensitivity (hs) assay within the conventional normal reference range has been found to be common among patients with coronary artery disease (CAD) and the magnitude of hs-troponin elevation predicts risk in both cardiac patients and general populations (1-6).

These observations have led to an increasing number of studies to assess the pathophysiological significance of elevations in hs-cTn, including studies that have investigated the relationship between exercise-induced ischemia and hs-troponin levels. A consistent finding is that higher resting hs-troponin levels predict a greater likelihood of inducible myocardial ischemia with exercise (7-12). Study of the effects of exercise and inducible ischemia on hs-troponin levels in control subjects and CAD patients, however, has led to discordant observations. For instance, Sabatine et al. (13) have reported a graded increase in hs-troponin levels with increasing ischemia in CAD patients; Axelsson et al. (9) found elevations in hs-troponin with exercise in both CAD patients and control subjects, but with substantially higher levels in their CAD cohort; and Lee et al. (12) have reported that whereas patients with exercise-induced ischemia had higher hs-troponin levels at rest, both ischemic and nonischemic patients had a similar rise in hs-troponin during exercise in their patient cohort. Accordingly, further study is indicated.

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In this issue of *iJACC*, Hammadah et al. (14) now address this issue through a novel study involving the evaluation of 587 stable CAD patients who underwent myocardial perfusion imaging during both mental stress testing, using a standardized public speaking task, as well as during conventional stress testing (i.e., exercise or pharmacological stress). All patients had measurements of hs-cTnI performed at rest and following both mental and conventional stress testing. Overall, 16% of patients developed ischemia during mental stress testing and 35% during conventional stress testing. The presence of elevated resting hs-cTnI levels in this study predicted a greater likelihood of observing ischemia during both mental stress and conventional stress testing. Conversely, higher resting hs-cTnI levels were noted among patients who manifested ischemia during mental or conventional stress testing compared with those without inducible ischemia. Based on these observations, Hammadah et al. (14) conclude that "it is likely that repeated episodes of myocardial ischemia during daily life, that are often silent, contribute to the observed sustained increase in resting hs-cTnI levels."

Of note, the actual correlation between the magnitude of mental stress-induced ischemia and hs-cTnI levels was only modest, even statistically,

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suggesting that caution should be exerted in drawing biological inferences from these data. Given this modest correlation, it is important to examine what additional factors might have influenced the results of the study. We will examine 3 potential sources of variability, including those pertaining to mental stress testing, potential technical factors, and pathophysiological considerations.

MENTAL STRESS TESTING

Initial interest in exploring ischemia during mental stress testing was an outgrowth of observations regarding the occurrence of myocardial ischemia during ambulatory electrocardiogram monitoring. A salient feature of such studies was the observation that a large proportion of ischemic episodes during daily life experience were occurring without chest pain (i.e., so-called silent ischemia) and at relatively low heart rate elevations compared with the threshold for inducing ischemia during laboratory exercise testing (15).

To assess whether mental stress might be a potential explanation for silent ischemia, we previously imaged, using radionuclide ventriculography, CAD patients during both exercise and four mental tasks: a math task; the word Stroop task; a public speaking task; and a reading task (16). Patients were imaged during each task. To make the public speaking personally relevant, patients were asked to honestly speak about personal faults or habits with which they were dissatisfied. Overall, mental stress-induced wall motion abnormalities occurred in 23 of 39 CAD patients (59%), but the personally relevant speaking task induced both more frequent and greater wall motion abnormalities than the less specific mental stressors did. Most mental stress ischemia occurred silently and at low heart elevations compared with exercise-induced ischemia. Since that time, public speaking has become a commonly utilized stressor to induce mental stress, but the nature of the speaking task has varied among studies. The present performance of mental stress testing with a public speaking task in 587 patients using myocardial perfusion imaging provides a rich opportunity to assess the significance of mental stress-induced ischemia in relation to other clinical variables and outcomes.

Just as clinicians evaluate the assessment of exercise-induced ischemia according to the intensity of physical exertion, assessing mental stress testing according to the intensity of the mental stress would also be useful. For the present protocol, patients were asked to imagine a situation in which a close relative had been mistreated in a nursing home. Subjects were then given 2 min to prepare a speech, and then to speak for 3 min in front of an evaluative audience. Thus, the task had 2 essential elements: an attempt to invoke emotional distress; and the induction of anxiety by having the speech given in front of the evaluative audience.

As research with mental stress ischemia advances, it would useful to characterize the adequacy of the mental stress, just as is done for exercise testing, in each patient. For instance, the intensity of the mental stress in this study could have been subject to patients' individual ability to vividly imagine the suggested emotional scenario, the degree of patient engagement during the mental stress protocol, and how stressed patients actually felt during the protocol. Observer evaluation of patients' participation and experience might also be useful.

TECHNICAL CONSIDERATIONS. Because the assessment of troponin changes elicited by stress testing is a relatively new but expanding area of interest, prospective study may be needed to determine standards of investigation that can be uniformly adopted among investigators. For instance, what is the optimal time to assess troponin elevations following exercise testing? In the present study, the investigators measured hs-cTnI levels at rest and 45 and 90 min after mental stress test and 45 min after conventional stress testing. Other investigators, however, have chosen to obtain troponin measurements at other temporal periods post-exercise. For instance, Sabatine et al. (13) measured troponin levels immediately post-stress and 2 and 4 h later. In their study, troponin values were increased at 2 h, but not immediately post-stress. In another study, Rosjo et al. (7) noted elevations in troponin immediately after exercise in patients without ischemia but increases after 4.5 h in their patients with inducible ischemia. In the most extensive study of this issue to date, Axelsson et al. (9) measured troponin levels at baseline and for each of 6 h after stress. Peak troponin values were observed after 5 h in their control group and after 6 h in their CAD patients. Given these disparate findings, standardization in the timing of post-stress hs-cTnI levels would be highly desirable.

Another technical issue requiring standardization is the criteria to be used to establish the presence of ischemia. In the present study, ischemia was defined by the presence of a summed reversibility score of $\geq$2 points. This represents a lenient definition for ischemia that would include patients with equivocal results in other laboratories (i.e., patients

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with summed reversibility scores of only 2 to 3). Thus, reanalysis of the current results according to a stricter definition of ischemia might be of interest.

PATHOPHYSIOLOGICAL CONSIDERATIONS

There is a growing understanding of the multifactorial determinants of hs-cTnI elevations. As Hammadah et al. (14) point out, these determinants include factors such as heart failure, myocarditis, pulmonary embolism, sepsis, and hypertensive crisis. In addition, various cardiac factors appear to increase the risk for observing elevations in hs-cTnI elevations in CAD populations, including reduced left ventricular ejection fraction, resting perfusion defects, reduced exercise capacity, left atrial size, and diastolic function (2,11,17). The multifactorial determinants of troponin elevations adds complexity to the present study due to the heterogenous nature of the study cohort. Among the patients, 31% had a history of prior myocardial infarction and 13% had a history of heart failure. The presence of resting wall motion abnormality, itself, manifested a moderate correlation with hs-cTnI levels in this study, comparable to that noted between ischemia and hs-cTnI levels. As Hammadah et al. (14) noted, resting perfusion defects and inducible ischemia appeared to be synergistic predictors of hs-cTnI elevations.

Atherosclerotic burden represents another mediating factor of hs-cTnI levels. In this study (14), however, the assessment of atherosclerotic burden was limited to just a composite angiographic measurement, the Gensini score (18). More recently, intravascular ultrasound (19) and coronary computed tomographic angiography (8,20) have been used to provide a more sophisticated comparison of atherosclerotic burden to hs-troponin levels, with evidence of positive associations. Notably, in a recent study, Korosoglou et al. (20) reported a high correlation between measurements of total noncalcified plaque burden and troponin measurements ($r = 0.79$), but further study is needed to assess the robustness of this finding. Such findings are important because atherosclerotic burden is also known to be a potent predictor of both clinical risk (21) and the induction of ischemia (22,23). Thus, it cannot presently be concluded with certainty whether the higher resting levels of hs-cTnI among patients with mental stress-induced ischemia is due to more recurrent daily life ischemia, as Hammadah et al. (14) postulate, or due to a higher atherosclerotic burden that leads to both elevated hs-cTnI levels and a greater likelihood of inducible ischemia, or to a synergy of these 2 mechanisms, and/or to other factors.

TROPONIN ELEVATIONS AMONG PATIENTS REQUIRING PHARMACOLOGICAL STRESS

An underemphasized aspect of the current study was the substantially higher levels of hs-cTnI noted among patients who required pharmacological stress in this study compared with those who could exercise. These results are of interest in light of data indicating that the requirement for pharmacological stress is a substantial predictor for increased risk among patients referred for stress myocardial perfusion imaging. Patients undergoing pharmacological stress testing tend to be older and sicker than exercise patients are, but even after propensity matching for age, sex, risk factors, and chest pain, they have an unexplained greater mortality risk than exercising patients do (24). Accordingly, further explorations of the relationship between troponin levels and factors governing the need for pharmacological stress testing could be of interest in defining the mechanisms that mediate an increased risk among patients who cannot exercise.

CONCLUSIONS

Hammadah et al. (14) have performed a large-scale study that confirms and extends the results of prior studies that have demonstrated that elevations in resting hs-troponin levels identify patients who are more prone to stress-induced ischemia, during both exercise and mental stress. Conversely, patients with inducible ischemia have higher resting hs-troponin levels. These and other observations further an emerging consensus that elevations of hs-troponin exists along a continuum of precipitants, ranging from the presence and magnitude of coronary atherosclerotic burden, to the induction of ischemia, development of acute coronary syndromes, and occurrence of myocardial infarction. Because the pathophysiological determinants of cTn levels are multifactorial, there is a need to standardize the methods for conducting laboratory investigations into the precipitants and measurements of troponin elevations during exercise and mental stress testing. Such standardization could lead to an enhanced ability to compare the results emanating from different medical centers and to study causal mechanisms.

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