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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.

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 pharmacologic 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, is that 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 stess testing with a public speaking task in 587 patients using myocardial perfusion imaging provides a rich opportunity to assess the signficance 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