Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop

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Session 2

1. Topic and Author

The Sensitive Heart- Visceral Pain Sensitivity and Chest Pain Without CAD.

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2. Where we stand in 2002. Overview/rationale for inclusion of topic.

Chest pain continues to be a common symptom reported by women to health care providers. Several survey studies, including WISE, have found that most women who undergo coronary arteriography do not have coronary artery disease that appears sufficient to explain symptoms. Although in some, the severity of obstruction within coronary arteries may be underestimated by visual assessment, in most an alternative explanation for pain must be sought. The debate that continues to this day is whether women (or men) who have angina-like chest pain -in the absence of CAD, spasm or cardiomyopathy- experience myocardial ischemia by some intramyocardial process, presumably microvascular dysfunction. WISE investigators reported changes in high energy phosphate signals by NMR spectroscopy, interpreted as ischemia, during relatively mild hand-grip exercise in a subset of women undergoing this test.[1] There was no correlation between normal versus abnormal phosphate spectral changes and results of endothelial testing or exercise nuclear perfusion imaging (exercise ECG responses were not reported). Thus, it is unclear whether women with such abnormal responses to stress can be identified with conventional noninvasive testing (for example, ischemic appearing ST segment depression that defines cardiovascular syndrome X) or have abnormal endothelial function, proposed to cause ischemia in this setting. Earlier this year, a group in the U.K. reported diminished increases in subendocardial relative to epicardial gadolinium uptake (as a marker of blood flow) by MRI during dipyridamole infusion in 20 patients (16 women) selected on the basis of a positive (ST segment depression) exercise EKG.[2]

Other groups, however, have not identified metabolic or hemodynamic evidence for myocardial ischemia during stress in patients with chest pain despite normal coronary angiograms, even when selected for a positive exercise tes (syndrome X)t.[3-5] The recognition that these patients commonly experience chest pain during cardiac catheterization with movement of catheters in the heart and injection of contrast media into coronary arteries has led to suspicion that altered visceral pain sensitivity may be of greater importance than ischemia in accounting for chest pain symptoms.[6-8] In this regard, adenosine or dipyridamole infusions to assess coronary vasodilator reserve commonly provoke severe pain in these patients.[9,10] In a group of 60 patients (40 women), we found that characteristic chest pain could be provoked by catheter movement, electrical stimulation of the right ventricle or atrium, or adenosine infusion in over three-quarters of the cohort.[11] In a treatment trial that followed, the tricyclic antidepressant imipramine reduced chest pain frequency in a blinded, randomized, placebo-controlled study. Although most patients had some evidence for psychiatric disability at baseline (especially panic disorder), there was no association between pain reduction and change in psychiatric testing over the course of the study.

Rosen and coworkers[12] have considered the possibility that central neural processing of sensory input from viscera might be important in understanding symptoms in this patient population. They measured regional cerebral blood flow (positron emission tomography) as an index of neuronal activity at rest and during dobutamine stress in 8 syndrome X patients (6 women) and 8 control subjects (5 women). Dobutamine precipitated severe chest pain and ST segment depression in all syndrome X patients, although echocardiography showed increased left ventricular contractility. Syndrome X patients and controls showed similar increases in blood flow in the hypothalamus, thalami, right orbito-frontal cortex and anterior temporal

lobes. In patients, but not controls, increased blood flow was also noted in the right anterior insula/frontal operculum junction. In a previous study of identical design but with coronary artery disease patients, dobutamine infusion provoked chest pain and echocardiographic evidence of myocardial ischemia: No increased blood flow in the right insula was noted in these patients with ischemia-provoked chest pain.[13] Thus, syndrome X patients have an altered pattern of cortical activation by visceral afferent signals, which may contribute to abnormal pain perception during cardiac stress even in the absence of ischemia.

3. Current challenges and the most important issues for future research

A major challenge for the ischemia enthusiasts is to link the findings reported by different groups with small numbers of patients to a coherent pathophysiology. That is, despite the reports cited above, it remains unknown whether endothelial dysfunction accounts for the endocardial flow limitation observed during dipyridamole-stimulated gadolinium MRI in some patients, and whether either are responsible for the high energy phosphate spectral abnormalities reported in the WISE cohort. From a clinical standpoint, we must determine whether abnormalities identified by testing with limited availability (cardiac MRI, NMR spectroscopy, endothelial testing) correlate with conventional stress testing (exercise EKG, stress echo, nuclear perfusion imaging), such that these more widely available tests may be used to identify those who truly have an ischemic syndrome to account for symptoms. Finally, we need to know what test identifies patients who will respond to anti-ischemic or other therapy, or who have a higher risk of cardiovascular events to justify its use. Major challenges for the visceral pain enthusiasts are to demonstrate a mechanism for altered visceral sensitivity and CNS afferent signal processing, and investigate targeted therapies that relieve symptoms with acceptable side effect profiles.

4. Current challenges in the areas of communicating messages to health care community, patients and the public

Three major challenges in the management of patients with angina-like chest pain despite normal coronary angiograms are: 1) Correctly identifying patients who have an ischemic syndrome who will respond to anti-ischemic or other specific therapies, 2) Demonstrating pathophysiologically plausible mechanisms for microvascular dysfunction, if the basis for ischemia, and 3) Devising an approach to the majority who do not have ischemia to account for symptoms, which may require input from psychologists/psychiatrists and specialists in chronic pain management.

5. Translating new findings to improved diagnosis and treatment/saving lives.

New testing modalities such as NMR spectroscopy and gadolinium cardiac MRI may identify patients whose chest pain is due to myocardial ischemia, and show treatment responses in properly designed clinical trials. Functional brain imaging studies may lead to understanding of the prevalence and mechanisms of altered visceral afferent sensory input and cortical activation, and be useful in testing therapies that might permit effective pain control.

6. References.

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