CLINICAL VIGNETTE

False Negative Nuclear Stress Test

Roman Leibzon, MD and Boris Arbit, MD

Case Report

An 86-year-old man presented to cardiology with exertional chest discomfort. His past medical history includes: diabetes, hypertension, hyperlipidemia, chronic kidney disease, paroxysmal atrial fibrillation, moderate aortic stenosis, and coronary artery disease (CAD) with prior myocardial infarction and stenting of the left circumflex and right coronary arteries. He describes recent onset of midsternal "burning sensation" which was present at rest and exacerbated with physical exertion. His physical exam was notable for a 3/6 systolic ejection murmur heard best at the right upper sternal border. EKG was unchanged and showed sinus bradycardia, right bundle branch block, left posterior fascicular block, and inferior infarct. Subsequently, patient underwent a Lexiscan Myoview nuclear stress test which showed no evidence of ischemia and normal systolic left ventricular function. However, during a follow-up visit, he reported a worsening of chest discomfort. Given documented CAD and persistent angina, he was referred for coronary angiography. Coronary angiography revealed 90% in-stent restenosis in the right coronary artery. Patient underwent repeat stenting of the right coronary with complete resolution of chest pain.

Discussion

Evaluation of obstructive CAD is generally divided into invasive and noninvasive approaches. Coronary angiography has remained the "gold standard" for evaluation of CAD.[1] However, coronary angiography is an invasive assessment of CAD and carries small, but significant morbidity and mortality (less than 0.1%).[2] Therefore, noninvasive testing is often the initial step in assessment of ischemic CAD.

Cardiac stress testing can be done in a number of ways, but a regular exercise stress remains the easiest and most available form. Adding imaging to stress testing increases the test accuracy therefore, echocardiographic imaging or nuclear imaging are often added to stress testing. CT coronary angiogram allows for visualization of the coronary anatomy while avoiding some of the invasive risks or cardiac catheterization. Accuracy of the above noninvasive testing is variable and affects test interpretation and usage.

Exercise Stress Test

An exercise stress test is performed while the patient exercises on treadmill or bicycle. Exercise stress testing increased cardiac oxygen demand. In the setting of severe coronary artery disease this increase in oxygen demand cannot be met resulting in myocardial ischemia which can be seen with characteristic ST changes and anginal symptoms. Exercise stress EKG is considered abnormal when there is >= 1 mm horizontal or down sloping ST changes in one or more leads which persists at 80 milliseconds after the J point.[3] EKG changes in Lead V5 – V6 appear to be the most sensitive in detecting ischemia.[4] A meta-analysis of 147 studies involving 24,074 patients which studied exercise-induced ST depression versus angiographic findings found mean sensitivity of 68% and mean specificity of 77% for diagnosis of severe CAD based on exercise stress testing.[5] It must be noted that accuracy of EKG stress testing in women is lower. A meta-analysis of women undergoing EKG stress tests to diagnose coronary disease showed sensitivity of 61% and specificity of 70%.[6]

Stress Echocardiogram

Stress echocardiography is performed using a treadmill, stationary bicycle, or a chemical agent to accelerate the heartrate. During a stress echocardiogram, a standard assessment of EKG and anginal symptoms is performed; however, in addition, echocardiographic imaging is also obtained before the stress test and at peak exercise. The echocardiographic imaging assesses for wall motion abnormalities, abnormal contractility and ejection fraction with exercise. For chemical stress testing, the most commonly used agent is dobutamine. If target heart rate cannot be achieved with dobutamine alone then atropine is added. Adding echocardiographic imaging increases the accuracy of an EKG stress test. A meta-analysis of stress echocardiography studies with a total of 1405 patients showed a sensitivity and specificity of 80% and 86% respectively.[7]

Cardiac Radionuclide Imaging

Nuclear stress testing utilizes techniques called single photon emission computed tomography (SPECT) or positron emission tomography (PET) to image the heart and assess myocardial perfusion based on nuclear tracer distribution within the myocardium. SPECT imaging utilizes 99m-Technetium radiolabeled agents or thalium-201. While PET imaging utilizes Rubidium-82 or 13N-ammonia. Imaging is traditionally obtained at rest and stress, the acquired images are compared to assess for perfusion defects. Exercise stress can be performed using a treadmill or a stationary bicycle. Vasodilatory stress is

unique to myocardial perfusion imaging and can demonstrate relative flow inequalities (with SPECT) or absolute flow decrease (with PET) within the myocardium. Common vasodilatory agents are adenosine, dipyridamole, and regadenoson. All achieved vasodilation by stimulating the A2A adenosine receptor.[8,9] Average myocardial blood flow increases 4-fold with maximal hyperemia with these vasodilatory agents.[10] Normal coronary circulation will demonstrate homogenous distribution of the nuclear tracer on myocardial perfusion imaging. Coronary arteries with severe stenosis will have impaired vasodilatation and will receive less flow during vasodilatation and therefore less of the nuclear tracer. On myocardial perfusion imaging these areas will have perfusion defects secondary to decrease in nuclear tracer uptake. A meta-Analysis of PET and SPECT myocardial perfusion studies (1344 and 1755 patient respectively) showed superior accuracy of Rubidium-82 PET. SPECT myocardial perfusion imaging showed sensitivity of 85% and specificity of 85% while PET imaging showed sensitivity of 90% and specificity of 88%.[11] In patients with relative contraindication for vasodilators stress (such as severe obstructive airway disease), pharmacological stress can also be performed using dobutamine with or without atropine protocol. A meta-analysis assessing the accuracy of dobutamine stress with SPECT myocardial perfusion imaging showed sensitivity of 88% and specificity of 74%.[12]

CT Coronary Angiogram

Using multidetector computed tomographic coronary angiography we are able to visualize the coronary anatomy with a less invasive approach than standard invasive coronary angiography. The accuracy of a CT coronary angiogram is variable but sensitivity for significant CAD is 85-99% with a specificity of 64- 90%.[13-15] The variability in accuracy of CT coronary angiography stems from a multitude of factors that can affect image quality such as heart rate, cardiac motion, breathing, and coronary calcifications.[15]

Conclusion

A multitude of noninvasive techniques are available to assess obstructive coronary artery disease. Modalities such as exercise stress testing, nuclear stress testing, stress echocardiography and CT coronary angiography are useful in assessing for obstructive coronary artery disease. Pretest probability should be integrated with assessment of CAD and increases the accuracy of the noninvasive testing for obstructive CAD.[16] However, all the above tests fall short when compared to invasive coronary angiography, which remains the gold standard in assessment for obstructive CAD.

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