

# Coronary Artery Disease: Stress Testing, Follow-up and Referral

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**Coronary artery disease remains a** leading health problem in the United States. It accounts for major morbidity and mortality among men and women. The **National Heart, Lung and Blood Institute (NHLBI)** reports that one in four deaths annually is directly caused by coronary artery disease.<sup>1</sup> How we diagnose and treat coronary artery disease is a common concern for primary care physicians. While this review will not address the social concerns that arise when normal aging is defined as “disease,” it will address three common questions that arise in the course of routine practice. First, what form of functional testing, (imaging vs. non-imaging) should be used in patient assessment? Second, how do we follow patients with stable coronary artery disease? Third, when should patients be referred to a cardiology subspecialist?

## **WHEN SHOULD EXERCISE TESTING WITH IMAGING (NUCLEAR, ECHO) BE USED INSTEAD OF EXERCISE TESTING WITHOUT IMAGING?**

In 1929, Masters and Oppenheimer first reported on the clinical significance of **electrocardiogram (ECG)** change, specifically ST segment change with stress.<sup>2</sup> Modern stress testing was born. The goals of stress testing need to be considered in a general framework prior to discussion of the specific options available to the practitioner. Stress testing is of greatest utility in two major settings: first, in the initial risk assessment of patients suspected of suffering from ischemic chest pain, and second, in evaluating patients with known disease who have had a significant change in symptomatology. Additionally, there is a role for stress testing in the diagnosis of stable coronary heart disease as well as in understanding prognosis after treatment for an acute cardiac event.<sup>3,4</sup>

In thinking about atherosclerosis, it is critical to note that it is a progressive natural process that occurs in the course of normal aging. While the presence of atherosclerosis does increase risk of cardiac

events, it is not the cause of myocardial infarction. This process is the result of plaque rupture and thrombus formation and is not well predicted by stress testing. (Even a high-risk stress test, in the setting of stable symptoms, imparts an annual risk of only 5%.) Thus, when we describe a stress test as being “positive” or “negative” we are not really describing whether or not atherosclerosis is present, but rather, if symptomatic patients are experiencing symptoms in relation to obstructive coronary artery disease. While there is prognostic information to be obtained regarding risk in relation to exercise duration, development of anginal symptoms—particularly at a low work load—blood pressure response to exercise, chronotropic response and extent of ECG change or size of perfusion defect, this data is frequently subsidiary to the primary question being asked: are the patients’ symptoms the result of coronary heart disease?

Stress testing is best understood as a function of probability statistics. The pretest probability for the presence of coronary artery disease affects the interpretation of the result. While Masters observed that ST segment depression was associated with the presence of obstructive coronary artery disease, the sensitivity and specificity of this test have subsequently been further evaluated. If there is a low pretest probability (<25%), then an abnormal test does not change the result. Similarly, a normal test in a patient with high pretest probability needs to be interpreted with caution. Stress testing is most valuable in patients with intermediate (to high) risk, where an abnormal result is most likely to reflect a true positive result. ECG changes with physical stress are a derivative function. Flow limitation leads to oxygen debt, leads to metabolic change at a cellular level, leading to electrical change that can then be observed on a macroscopic level through ECG monitoring. ECG change with stress is not 100% sensitive or specific for detecting obstructive coronary disease. Factors beyond ischemia affect exercise

ECG, including baseline abnormality on the surface ECG (ST segment abnormalities, **Wolff–Parkinson–White syndrome (WPW)** or **left bundle branch block (LBBB)** for example) and medication affect. This has led to the development of additional techniques to improve our diagnostic accuracy.

Perfusion imaging was developed in an effort to improve the diagnostic accuracy of cardiac stress testing. Radiopharmaceuticals share the basic property that they are taken up in the myocardium in proportion to blood flow. Understanding that myocardial blood flow is a regional phenomenon serves as a background for understanding the role of this technique. At rest, even in the presence of obstructive coronary artery disease there should not be flow disparity. With stress, myocardial demand increases and flow may then increase disproportionately. Imaging agents can then “track” this flow. Flow disparity, a defect, will be evident with stress, and resolve with rest when flow deficit resolves. (Assuming there has been no prior damage. Fixed defects then reflect infarction, rather than ischemia.) It is important to keep this in mind when we try to sort through the benefits of choosing one form of stress testing modality over another. Perfusion imaging does improve sensitivity for detection of ischemia with the following caveats. Since we are comparing “relative” flow, there can be false positives in the setting of balanced defects. Since these images are processed, there are multiple areas where artifact can be introduced leading to “false” positive results. Currently used radiopharmaceuticals emit gamma rays. Error can be introduced throughout image processing as it relates to image counts, soft tissue attenuation, and background subtraction.

Stress echocardiography developed similarly to perfusion imaging to aid in the diagnosis of significant obstructive coronary artery disease. Understanding how stress echo is done serves as a basis for understanding how and why it might be preferable to perfusion imaging or to

treadmill stress testing alone. Recognizing the problems associated with false positive and false negative stress tests, and in an effort to avoid the risk and expense associated with radiopharmaceuticals, stress echocardiography looks specifically at wall motion both at rest and at peak stress. In patients without a prior myocardial infarction, wall motion should be normal at rest. With stress, myocardial ischemia leads to regional wall motion abnormality, specifically, hypokinesis, and, if the ischemia is severe enough akinesis or even dyskinesis of the region subtended by the obstructed artery. Hence, when added to the stress ECG alone, wall motion assessment improves both sensitivity and specificity for detection of ischemia. Stress echo avoids the need to administer radioactive agents and is therefore “easier” and “less expensive”. Due to the fact that the myocardial function is directly visualized, certain imaging artifacts that plague perfusion imaging, such as overlying soft tissue or artifact due to processing affected by count ratios and background subtraction, are avoided. This is not to say that stress echocardiography does not have its own limitations. Images at peak stress must be obtained rapidly (given that ischemia is transient, the moment that stress is terminated, ischemia should begin to resolve). Imaging windows can be difficult to obtain. Echo is affected by respiratory pattern and to a certain extent by overlying soft tissue. Finally, interpretation of stress echoes can be quite challenging and requires an advanced degree of expertise that is not universally available.<sup>5</sup>

Beyond answering the question as to whether or not a patient's symptoms are related to the presence of obstructive coronary artery disease, a great deal of information can be obtained simply by having a patient walk on a treadmill. For this reason, it is almost always preferable to consider treadmill or cycle ergometry as the mode of stress. Patients with a normal functional capacity who are able to exercise into stage 4 of a Bruce protocol, (an exercise effort that is roughly equivalent to 10 metabolic equivalents), have an excellent prognosis from a cardiac standpoint (<1% risk of cardiac event at one year). This is independent of whether or not additional imaging is performed. Equally true is that patients with poor functional capacity have a worse outcome whether

or not imaging is added. Additional data to aid the clinician including blood pressure and heart rate response, time to development of symptoms, time to onset of ECG change are all obtained regardless of the modality. Furthermore, the extent of the physiologic stress will also strongly impact ability to detect ischemia. Sub maximal stress may not provoke ischemia. Sensitivity of all stress testing depends on generation of an adequate double product (peak systolic pressure x heart rate). Use of common medications such as antihypertensives or beta blockers might inhibit the ability of all modalities to detect ischemia. Consideration regarding the specific question being assessed will affect whether or not testing is being performed in the presence of current therapy.

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### **For patients who cannot exercise, stress testing can still be performed.**

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Nuclear imaging provides additional assessment, beyond non-imaging treadmill stress testing. Gated imaging, when it can be performed, gives information regarding wall motion as well as estimated ejection fraction. (Ejection fraction less than 45% being an independent factor of increased risk.) Ventricular volumes, right ventricular size, lung uptake of tracer, and extra cardiac tracer uptake can all be seen. Incidental findings of malignancies have been made in the course of cardiac exams. So too, stress echo provides additional information regarding valve structures, chamber sizes, ejection fraction and regurgitant lesions. (Complete echocardiographic study, involving Doppler assessment of valvular lesions is no longer routinely done concomitantly with stress testing. Most labs perform either a complete resting study, or a more focused study in the setting of stress echo. Comprehensive resting exams are more time consuming and are not reimbursed if done at the same time as a stress study.)

For patients who cannot exercise, stress testing can still be performed. Pharmacologic agents “simulate” physiologic stress. For perfusion imaging, adenosine, or a newer more cardiospecific agent,

regadenosine, is generally the stressor of choice. These agents, through direct stimulation of adenosine receptors cause coronary vasodilatation and a supraphysiologic increase in coronary blood flow. Radiopharmaceuticals injected at peak pharmacologic stress can then track flow and detect ischemia just as you would under physiologic stress. This technique has been shown to be extremely safe and able to detect ischemia with a great degree of sensitivity and specificity. Similarly, dobutamine has been used in stress echo. At supratherapeutic doses of this beta agonist, myocardial ischemia can be provoked. Occasionally atropine will need to be added to provide adequate stress. Safety as well as sensitivity and specificity of this technique are equally high.

When choosing between stress test options it is important to note that regardless of the chosen modality, the greater the degree of obstructive disease, and the more proximal the obstruction, the more likely it will be detected. Left main coronary artery disease, or a greater than 70% stenosis of a major epicardial vessel is likely to be detected by any of the available techniques. The greater the extent of obstructive disease, the greater the sensitivity to detect it.

Are there times when a stress test is contraindicated? Given that these tests are diagnostic rather than therapeutic, and that we follow the maxim to “do no harm”, there are obvious times when all agree stress testing is to be avoided. Acute infarction and unstable angina are two such. Most experts agree that exercise testing in the setting of severe aortic stenosis should only be done with the greatest of caution. In the era of frequent myocardial revascularization and intervention, we generally advise *against* vigorous exercise and maximal stress testing within the first few weeks after revascularization (particularly with drug eluting stents). There is some disagreement among experts as to how soon patients can safely exercise post stenting. Most agree that earlier than two weeks is too soon and greater than four weeks is certainly safe.

In summary, when choosing which test to order physicians need to think about the question they are asking and the particular risk group into which the patient falls, before deciding on which test to order. Physicians need to determine

if the pretest probability is high enough to warrant a stress test at all. It is always preferable to have patients exercise, given the additional information that is derived. If the patient has an abnormal baseline ECG, or if they are unable to exercise on a treadmill due to other physical factors, then alternative stress testing modalities must be employed. Additionally, it is well recognized that stress testing in women has a lower diagnostic accuracy. Imaging, in addition to exercise improves diagnostic accuracy but at additional cost. Some authors have suggested, and I agree, that it is reasonable to begin with a treadmill stress alone in women if they have a normal resting ECG and an intermediate risk for **coronary artery disease (CAD)**. Good functional capacity without ECG change, a negative test, carries low risk and no further testing is required. In this approach we would anticipate that 1/3 of patients would require no additional testing. An abnormal test, without imaging, however, would require further assessment. In any case, patients with abnormal resting ECGs need additional imaging (perfusion or echocardiographic). Patients who cannot exercise need pharmacologic stress and then additional imaging.<sup>6</sup>

#### **HOW SHOULD PATIENTS WITH STABLE CAD, INCLUDING HISTORY OF MYOCARDIAL INFARCTION (MI), BE FOLLOWED, INCLUDING THE ROLE OF STRESS TESTING?**

How then do we follow patients with coronary artery disease? Is there a role for “routine” stress testing? In patients with coronary artery disease, much like patients with any chronic condition, “following” patients involves pursuing strategies shown to reduce risk of future events. Risk reduction is not the same as risk elimination. Testing itself does not

eliminate risk; nor does it *prevent* heart attack. Strategies for risk reduction are well known and they include smoking cessation, blood pressure control, control of blood sugar and cholesterol lowering (in appropriate high-risk groups, most notably patients with prior vascular events). “Routine” stress testing does not appear in the list of known effective strategies to reduce risk (nor does CT scanning, MRI and even percutaneous intervention). In following patients, beyond efforts to control risk factors, a history that defines activity level and seeks to elicit the presence or absence of signs and symptoms of unstable or progressive disease may be the clinician’s single most important tool in long-term follow up.

#### **WHEN SHOULD A PATIENT WITH CORONARY ARTERY DISEASE BE REFERRED TO A CARDIOLOGIST?**

Finally, in approaching a patient with chronic illness it is important to consider when to ask for consultation input. While it seems obvious to say that it is almost never wrong to ask for a second opinion when questions arise, particularly in a field that is out of one’s area of special interest or ongoing expertise, there are times when a consultation is warranted. In the setting of an acute change in symptom pattern, where intervention is required to immediately affect outcome, consultation is indicated. But what about in the setting of managing chronic coronary artery disease in general, and in selecting a modality for stress testing in specific? The answer to the first question will depend on the clinician’s experience, time and interest. Patient factors, too, will often drive a request for consultation. And there is a range of acceptable practice patterns that will inform that choice.

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#### **Disclosure of Financial Interests**

The author and/or spouse/significant other has no financial interests to disclose.

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