RISK STRATIFICATION FOR CORONARY ARTERY DISEASE USING PHARMACOLOGICAL STRESS TESTS

Stephanie EL-HAJJ1, Fadi G. HAGE2


ABSTRACT: Cardiac stress testing is frequently used for diagnosis of coronary artery disease and for risk stratification which can facilitate decision making and help in the overall management of patients with known or suspected coronary disease. Exercise remains the preferred stress modality and should be performed when feasible but it is often contraindicated, impractical or unable to provide the needed information. In these circumstances pharmacologic stress tests can provide a wealth of prognostic data and should be performed instead of non-diagnostic or suboptimal exercise stress tests. Here we will review the use of pharmacologic stress tests including the indications for ordering them and the different stress agents and imaging modalities that can be utilized with emphasis on practical information that the primary care physician and general practitioner need on a daily basis in their practice.

Keywords: myocardial perfusion imaging, pharmacologic stress test, coronary artery disease, risk stratification

The evaluation of patients presenting with chest pain or equivalent symptoms thought to be secondary to coronary artery disease (CAD) will often include some form of stress testing. These tests provide prognostic information beyond answering the question of whether the symptoms are cardiac in origin or not. Stress tests are also ordered for risk stratification in the absence of symptoms such as in individuals undergoing peri-operative evaluation and those deemed to be at high risk of cardiac events (ex: diabetes mellitus, strong family history of CAD) [1-2]. Risk stratification using stress tests is not only a gateway for coronary angiography but can also facilitate decision making and help in the overall management of patients with known or suspected CAD. There is a wide array of available stress tests with varying diagnostic and prognostic values, strengths and limitations for the practicing physician to choose from [3]. The pharmacologic stress tests (PSTs) will be discussed here with special emphasis on when to order a PST, what to order, and the wealth of prognostic data provided by PSTs.

WHEN TO ORDER A PHARMACOLOGICAL STRESS TEST?

Generally speaking, exercise stress is preferable to pharmacologic stress since it provides valuable information with regard to the functional capacity of the individual and should be performed when feasible [4]. PSTs should be considered in individuals unable to exercise or when there is suspicion that they will be unable to reach at least 85% of their age-predicted heart rate (220 - age) and five metabolic equivalents. Occasionally exercise stress tests are converted to PSTs when the tested individual is unable to reach these targets. Conditions in which pharmacologic stress is used instead of exercise include, but are not limited to, peripheral vascular disease, deconditioning, pulmonary disease, arthritis, ampu-
exercise there is no real ischemia). Myocardial ischemia of the stenosed vessel (i.e. perfusion defect, but unlike with exercise) may occur despite increased flow even in injection of vasodilator causing heterogeneity of flow between the stenosed and non-stenosed vessels after this coronary flow reserve is utilized to maintain resting myocardial blood flow. In a coronary arteriole with hemodynamically significant stenosis part of increase in myocardial oxygen demand. In a coronary vessels causing hyperemia (3- to 5-fold) without an endogenous production of adenosine causes direct vasodilation of the coronary arterioles with up to 3-fold increase. Vasodilators can be safely used in these patients. Tor agonists can be safely used in these patients.

In evaluating a patient for noninvasive stress imaging it is important to assess the pretest probability or the likelihood of having CAD. Age, gender and chest pain are the most powerful predictors of CAD; other predictors include diabetes mellitus, smoking, hypercholesterolemia, and Q waves or ST-T segment changes on resting ECG. A global risk score can be estimated using models such as the Framingham Risk Score or the European Risk Score to allow for risk stratification of patients into low, intermediate or high risk before considering stress imaging. In low and high risk patients, the test will not result in a great difference between the pretest risk estimation and the posttest probability, rendering tests costly and ineffective. Patients that would benefit the most from noninvasive imaging and risk stratification are the ones with intermediate pretest probability since the test would add the greatest amount of information by risk stratifying a large proportion of them into the low and high risk subsets.

WHICH STRESS AGENT?

PSTs can be performed using coronary vasodilators or chronotrope/tonotrope agents.

Vasodilators

The most commonly used vasodilators include adenosine, dipyridamole and adenosine receptor agonists (ex: regadenoson and binodenoson). During exercise, endogenously produced adenosine causes direct vasodilation of the coronary arterioles with up to 3-fold increase in blood flow. The vasodilator agents work by stimulating adenosine receptors and vasodilating coronary vessels causing hyperemia (3- to 5-fold) without an increase in myocardial oxygen demand. In a coronary artery with hemodynamically significant stenosis part of this coronary flow reserve is utilized to maintain resting perfusion. This results in a difference in vasodilation between the stenosed and non-stenosed vessels after injection of vasodilator causing heterogeneity of flow and a ‘perfusion defect’ despite increased flow even in the stenosed vessel (i.e., perfusion defect, but unlike with exercise there is no real ischemia). Myocardial ischemia and/or ST segment depression can occur if there is a decrease of flow distal to the stenosis secondary to intercoronary steal and/or steal from the endocardium to the subepicardium where there is higher vasodilatory reserve.

Adenosine is by definition a non-selective adenosine receptor agonist. Since it has a half-life measured in seconds it has to be administered as a continuous infusion. Common side effects include ativoventricular block, hypotension, bradycardia, bronchospasm and other minor side effects such as flushing, nausea, dyspnea and headache.

Dipyridamole blocks the reuptake of adenosine which effectively inhibits its breakdown and increases its tissue concentrations. Dipyridamole has a slower onset of action and a much longer half-life than adenosine and thus more frequently requires administration of aminophylline to reverse its side effects. Some laboratories use low-level exercise supplementation with vasodilators to decrease side effects and improve image quality by reducing liver activity. Exercise supplementation should be avoided in patients with LBBB and those with right ventricular pacing. It is important to note that adenosine (and therefore dipyridamole) can commonly induce chest pain during the test by activating A1 receptors in the heart but unlike with exercise this is not a prognostic indicator. Regadenoson, a selective A2A receptor agonist, has been shown to be non-inferior to adenosine for the detection of reversible perfusion defects and to have a better side-effect profile likely secondary to its selectivity. Regadenoson has a much longer half-life compared to adenosine permitting its administration as a single intravenous bolus thus greatly simplifying the performance of vasodilator PST.

Current guidelines recommend that caffeine and other methylxanthines (ex: aminophylline, theophylline) be withheld for at least 12 hours prior to vasodilator stress myocardial perfusion imaging (MPI) and list this as a contraindication for performing the test. This recommendation has been recently questioned since most, although not all, studies have shown no effect of caffeine ingestion on MPI. We have recently proposed a practical approach to this common scenario in which patients are advised to abstain from caffeinated products the morning of the stress test. In patients who ingested one cup of coffee more than one hour prior to the test, the PST can be performed rather than cancelled or delayed. In patients who ingested larger quantities of caffeine we proposed that the rest MPI be performed first, to allow for serum caffeine levels to fall, followed by stress MPI.

Although adenosine and dipyridamole should be avoided in patients with active bronchospasm or reactive airway disease since by activating A2B and A3 receptors they may cause prolonged bronchospasm refractory to treatment, recent studies using regadenoson and binodenoson have demonstrated that A2A receptor agonists can be safely used in these patients.
Dobutamine
Dobutamine is a synthetic catecholamine that increases heart rate and myocardial contractility thus increasing oxygen demand. Onset of action is within two minutes of IV infusion. Generally it is used when vasodilators are contraindicated. Atropine is added when the optimal heart rate is not achieved at peak dose of dobutamine, especially in patients on β-blockers. This combination can produce up to fivefold increase in myocardial blood flow [32]. Dobutamine should be avoided in patients with recent myocardial infarction/unstable angina, significant aortic stenosis, hypertrophic obstructive cardiomyopathy, atrial tachyarrhythmias with uncontrolled ventricular response, ventricular tachycardia, uncontrolled hypertension and abdominal aortic aneurysm.

WHICH IMAGING MODALITY?

When deciding what modality to use, sensitivity, specificity, accuracy, prognostic value, cost-effectiveness, radiation exposure, patient comfort, availability and expertise in performance and interpretation of each modality have to be taken into consideration. The most widely used and available PSTs include MPI and two-dimensional echocardiography (2DE). Although opinions differ with respect to the superiority of either modality in some or all of these attributes, some studies have suggested that MPI has a higher sensitivity while 2DE has better specificity for detection of CAD [33-35]. It is generally felt that both tests provide similar prognostic value although the prognostic data with MPI is more robust. Practically, these modalities should be treated as providing comparable information and therefore the decision should hinge on local availability and expertise except in particular situations. Radiation exposure with MPI has received intense scrutiny recently [36]. While the benefits of MPI far outweigh the small risk of radiation exposure when appropriately used, it may be prudent to order 2DE in young individuals, and especially young women, due to the cumulative risk of radiation exposure on cancer incidence. One method to decrease radiation exposure with MPI is to perform the stress portion of the test first and if it is normal omit the rest portion. The advantages of stress-only MPI have been recently summarized [37]. This imaging protocol can effectively shorten the length of PST and decrease radiation exposure without compromising the diagnostic and prognostic information derived from the test [38]. Good echocardiographic windows are essential for 2DE and as such MPI is preferable in obese individuals and those with chronic obstructive lung disease in whom windows are often suboptimal.

Myocardial perfusion imaging
There is extensive data on the use of adenosine (and dipyridamole) MPI for detecting CAD and for risk stratification [39]. Adenosine MPI has been shown to add incremental prognostic value over clinical data and to permit adequate risk stratification into risk subsets. At peak coronary hyperemia a nuclear tracer is injected and imaging is performed. Most MPI today is performed with single-photon emission computed tomography (SPECT) which adds 3-dimensional information and perspective to the traditional planar imaging. Positron emission tomography (PET) is being increasingly used for MPI since as compared to SPECT it provides higher spatial resolution, enhanced image quality and quantitative rather than relative assessment of coronary blood flow [40].

MPI is usually obtained to assess myocardial perfusion. A normal MPI confers an excellent prognosis. As previously mentioned patients referred for vasodilator MPI have a higher pretest probability for CAD than those referred for exercise MPI, and therefore, have a slightly higher risk for major adverse cardiac events despite a normal study (1-2%/year for vasodilator stress vs. < 1% for exercise) [41-42]. Recent data confirms a similar low cardiac event rate in patients with normal MPI using regadenoson to those using adenosine [43]. This provides further assurance that the similar diagnostic accuracy of regadenoson vs. adenosine MPI seen in the clinical trials is translated into comparable prognostic information [22-23]. The presence and extent of perfusion abnormalities on MPI confers a significantly elevated risk of cardiac events that is several folds higher than that seen with normal perfusion (Table I). The extent of reversible defect is associated with risk of myocardial infarction while the extent of overall defects provides better prognostication for cardiac death [10]. A high-risk MPI usually denotes the presence of a large defect size or defects in more than one coronary territory (multi-vessel disease). Perfusion defects, and their reversibility, can be assessed visually using a semi-quantitative scoring system that gives scores of 0 (normal perfusion) to 4 (absent uptake) depending on severity of perfusion defect for each of 17-segments of the left ventricle (LV). The score can be derived for the stress images (summed stress score) and rest images (summed rest score), and by subtracting these scores an assessment of defect reversibility.

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**TABLE I**

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<th>Established prognostic indicators on PSTs associated with HIGH RISK</th>
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<tr>
<td>Perfusion abnormality</td>
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<td>(presence, extent and severity including multi-vessel distribution)</td>
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<td>Depressed left ventricular ejection fraction</td>
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<td>Left ventricular mechanical dysynchrony assessed by phase analysis</td>
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<td>Transient ischemic dilation with perfusion abnormality</td>
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<td>Blunted heart rate response to adenosine or adenosine receptor agonist</td>
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<th>Indicators on PSTs shown to be PROGNOSTICALLY UNIMPORTANT</th>
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<tr>
<td>ST-segment depression with normal perfusion in patients undergoing vasodilator stress</td>
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<td>Transient ischemic dilation with normal perfusion</td>
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can be obtained (summed difference score) [44]. Automated softwares can be used to derive a quantitative assessment of perfusion defect extent (as a percent of LV) and severity [44]. A large perfusion defect involves more than 20% of LV and/or has a summed stress score greater than 8.

In addition to perfusion abnormalities, LV ejection fraction (LVEF) derived by gated SPECT techniques provides incremental prognostic information. The lower the LVEF the higher the event rate and the worse the outcome. The association of LVEF with cardiac outcome is log-linear in nature and an LVEF < 40% usually signifies high-risk MPI [10]. Another high-risk feature is the presence of transient ischemic dilation (TID) of LV with stress. TID is thought to be related to decrease in sub-endocardial blood flow during stress and is a strong independent predictor of cardiac events [45]. While the presence of TID is usually associated with severe CAD and presence of perfusion abnormality, recent studies show that TID in an otherwise normal MPI is not a marker of increased risk (Table I) [46-47].

ST-segment depression during vasodilator MPI has been associated with increased risk [48]. Since ST depression is thought to be related to myocardial ischemia caused by coronary artery steal, it is less commonly seen with vasodilator stress vs. exercise and when present it is usually accompanied by abnormal perfusion on imaging. Patients with normal perfusion imaging who have ST-segment depression on ECG have been shown to have a benign outcome [49-51]. Interestingly, the vast majority of these patients are women suggesting a gender-effect on ST-segment response to stress. This mirrors the lack of prognostic significance of ECG changes during exercise when perfusion is normal, a phenomenon also mostly seen in women [52].

Another variable on vasodilator MPI that has been recently recognized to be associated with risk is the change of heart rate during the test [53]. Activating the A2a receptor (with adenosine, dipiridamole, or regadenoson) causes an increase in heart rate due to direct stimulation of the sympathetic nervous system. A blunted heart rate response (indicating cardiac autonomic dysfunction) during vasodilator MPI has been shown to be independently associated with poor outcome even after controlling for traditional MPI findings (perfusion and LVEF), diabetes mellitus, and other variables [54-56]. A low heart rate response predicts poor outcome while a robust response is associated with low event rate even in the presence of other risk factors. This simple marker routinely obtained during vasodilator stress can help effectively risk stratify various subsets of patients across the spectrum of pretest risk.

Two-dimensional echocardiography
This testing modality is based on the posit that myocardial ischemia induces transient worsening in regional LV wall thickening. Myocardial ischemia on 2DE is therefore represented by worsening of function with stress in a region contracting normally at baseline [57]. Since wall motion abnormalities occur earlier in the ischemic cascade than ECG changes but after myocardial perfusion abnormalities, 2DE has sensitivity for CAD detection that is intermediate between stress ECG and MPI. 2DE with dobutamine offers several advantages over MPI. It allows for assessment of valvular function, has lower cost, shorter testing time and therefore higher throughput through the laboratory and decreased patient discomfort, and avoids use of ionizing radiation. Compared to MPI which is more reproducible because of semi-automated computer quantification, 2DE is more operator dependent and is therefore more adversely affected by inter-observer variability (not only physician reading the study but also the technician performing the study) [58]. Dobutamine 2DE has similar sensitivity and accuracy for detection of CAD as exercise 2DE [57]. Prognostically, a negative dobutamine 2DE indicates an estimated mortality of less than 1% per year [59]. The presence of myocardial ischemia and the extent of abnormality represented by the number of abnormal territories at peak stress is an independent predictor of cardiac events [57, 60]. However, administration of dobutamine to high-risk patients is associated with more side effects than vasodilators. 2DE can also be used with vasodilator stress and ultrasound contrast to assess myocardial perfusion. Although this technique is theoretically appealing since it allows for the detection of perfusion and wall motion abnormalities using the same protocol, it has not gained widespread use since it does not offer any real advantages over vasodilator MPI which is more sensitive for detection of perfusion abnormalities and can also gauge wall motion using gated studies.

Magnetic resonance imaging
Cardiac magnetic resonance imaging can be performed with dobutamine or vasodilators for assessment of wall motion abnormalities and myocardial perfusion. This modality can help determine cardiac anatomy, function, perfusion and viability and it has been shown to have good diagnostic accuracy for detecting significant CAD and forecasting prognosis [61]. It has superior sensitivity for detection of subendocardial myocardial infarction and ischemia than MPI [62]. Although cardiac magnetic resonance imaging has great promise for being a ‘one-stop shop’ for evaluation of patients with suspected CAD, especially since it does not use ionizing radiation, it is currently limited by several factors. First, it is not recommended in patients with implanted ferromagnetic devices (pacemakers and cardiac defibrillators). Second, its use is limited by patients’ weight, claustrophobia and presence of arrhythmias. Last, it has limited availability and carries extra expense.

Computed tomography
Cardiac computed tomography is widely used for assessment of coronary anatomy and quantitative measurement of coronary calcium but emerging data suggest that it may be used for assessment of myocardial perfusion with vasodilator stress [63]. This hybrid technology is enticing
since it can simultaneously visualize coronary artery anatomy and myocardial perfusion allowing for functional assessment of coronary artery stenoses.

SPECIAL POPULATIONS

Some special patient populations warrant specific consideration while ordering, performing and interpreting PSTs. While a complete discussion of the use of PST in these populations is beyond the scope of this review we will address some pertinent points relating to these populations.

Diabetes mellitus

CAD is a major cause of death in diabetes mellitus. Various imaging modalities have been evaluated in the diabetic population and have been shown to be diagnostically similar in sensitivity and specificity for CAD detection as in the general population [64]. It is important to recognize that although diabetes is considered a CAD-risk equivalent, there is a spectrum of risk in diabetes, and risk stratification is possible in this population. Multiple studies have demonstrated that the presence and extent of myocardial ischemia add incremental prognostic value over clinical risk factors and stress ECG for the assessment of cardiac death and non-fatal MI. However, diabetes patients with a normal PST have an increased risk compared to non-diabetes patients with normal studies (residual risk). A recent study suggests that the increased cardiac risk seen in diabetes may be confined to those with chronic kidney disease [65].

Chronic kidney disease

Renal disease, extending from mild chronic kidney disease to end-stage renal disease, is an established cardiac risk factor [66]. The association of chronic kidney disease with multiple comorbidities limits functional capacity or prohibits exercise and necessitates PST in many instances. 2DE and MPI PST have been shown to be useful for risk stratification in chronic kidney disease. Hakeem et al. reported that patients with normal MPI who have chronic kidney disease have an annual cardiac death rate that is three times higher than patients with no kidney disease [67]. In their study, worsening perfusion defects were associated with worse outcomes across the spectrum of renal function and the presence of chronic kidney disease added prognostic value to the perfusion information. The prognostic utility of MPI in end-stage renal disease has been established in multiple studies and an abnormal MPI has been shown to provide better prognostication than the severity of angiographic CAD in this population [68]. An additional powerful prognostic factor on MPI in end-stage renal disease is a low LVEF [69].

Older adults

Cardiovascular risk is strongly age-dependent. As such older adults experience an exaggerated burden of cardiac disease compared to their share of the population. With increasing mean age of populations all over the world these trends are only expected to worsen. Older adults tend to have multiple comorbidities and physical deconditioning that make the utilization of PSTs more pertinent in this population. Studies have revealed that myocardial ischemia and LV systolic dysfunction continue to provide incremental prognostic data in older adults and can effectively risk stratify this patient population and guide management [70-71].

CONCLUSIONS

Exercise stress testing remains the preferred testing protocol but PSTs constitute an increasing proportion of performed stress tests worldwide. This trend is related to the aging of societies and to increasing comorbidities in individuals referred for testing. Thus, in a larger number of patients exercise stress is impractical, contraindicated, or is unable to provide the needed information. It is therefore essential for the referring physician to be cognizant of the wealth of prognostic data provided by PSTs and the intricacies of the various modalities and stress agents available to extract full benefit of performed tests in a particular patient.

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