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Stress Testing and Its Role in Coronary Artery Disease

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1.Introduction

Coronary Artery Disease (CAD) is the single leading cause of death of men and women in the Unites States. It accounts for about one-third of all deaths in subjects over age 35. The 2010 Heart Disease and Stroke Statistics update of the American Heart Association reported that 17.6 million persons in the United States have CAD, and that the 2006 overall death rate from cardiovascular disease was 262.5 per 100,000. CAD caused about one of every six deaths in the United States in 2006. From 1996–2006, the number of inpatient discharges from short stay hospitals with CAD, as the first listed diagnosis, increased from 6,107,000 to 6,161,000 discharges. The estimated direct and indirect cost of CAD for 2010 is $503.2 billion ($503.2 billion in equivalent Euro) (AHA, 2000). Being able to identify patients with suspected CAD early will help drive down hospital costs and ultimately decrease mortality and morbidity. Stress testing has emerged as the sole non-invasive method for risk stratifying patients with suspected CAD.

Apart from highlighting the salient advantages and disadvantages of various stress testing modalities, we will review which patients should undergo stress testing based on appropriateness criteria. Each patient needs to be managed separately based on their risk factors for significant CAD ultimately identifying those who may be at increased risk for the devastating sequeale of CAD such as acute myocardial infarction (AMI) or death.

2. Assessment of coronary artery disease risk

Identifying traditional, modifiable, and non-modifiable risk factors can help risk-stratify patients into low, intermediate, and high risk for CAD and cardiac death. Modifiable risks include hyperlipidemia (HLD), tobacco abuse, hypertension, diabetes mellitus (DM), physical inactivity, and obesity. Non-modifiable risk factors include a family history of CAD in first degree relatives under the age of 60, advanced age, and male gender (Kannel, 1976).

The frequency and predictive value of five major risk factors (hypertension, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, glucose intolerance, and smoking) was evaluated in a study of white non-Hispanic individuals without CAD in the Framingham Heart Study and the Third National Health and Nutrition Examination Survey (NHANES III) who were 35 to 74 years of age. (Pryor, 1993).

Advanced obstructive CAD can exist with minimal or no symptoms, and can progress rapidly. The first clinical manifestation could be (MI), unstable angina, or sudden cardiac death. The rationale for early detection of CAD is that detection during the subclinical stages of the disease might allow for the reliable identification of subjects at increased risk of an adverse cardiac event. Data from more than 10,000 subjects who participated in the Multiple Risk Factor Intervention Trial (MRFIT) and the Lipid Research Clinic's Coronary Primary Prevention Trial (LRCPPT) found that the presence of asymptomatic ischemia detected during baseline treadmill exercise testing predicted an increased risk of coronary events and cardiac death at 7 to 10 year follow-up (Rautaharju, 1986; Ekelund, 1989). The relative risk of an abnormal exercise test is greatest in patients with underlying risk factors for CAD, such as smoking, hypertension, HLD, and DM.

While there is general consensus that screening is not necessary for asymptomatic patients at low risk for CAD, there may be certain groups in which screening is warranted. Although the available data are not strong enough to reach consensus on the identity of these special groups, many clinicians perform periodic exercise electrocardiogram (ECG) tests in asymptomatic individuals with multiple coronary risk factors including: HLD, systolic blood pressure greater than 140 mmHg, diastolic blood pressure greater than 90 mmHg, smoking, DM, and a history of premature AMI or sudden cardiac death in a first-degree relative under age 60. A positive test in such patients is associated with an increased risk of subsequent AMI and death (Rautaharju, 1986; Ekelund, 1989).

When starting to screen patients for CAD, there is no single ideal test. Based upon the available data, easy accessibility, and cost considerations, most would deduce that initial screening with exercise ECG testing is the most practical approach in high-risk individuals who can exercise and who do not have ECG abnormalities that can limit the detection of ischemic changes. Additionally, an exercise test provides information about the exercise capacity, which may be more predictive of outcome than ST segment changes (Roger, 1998).

The predictive value of an abnormal screening exercise test is determined by the presence or absence of risk factors for CAD. In addition, treadmill scores have been devised to estimate patient prognosis according to test results. The most popular validated treadmill score comes from Duke University and is based upon data from 2758 consecutive patients with chest pain a median age of 49 (Mark, 1987). The Duke treadmill score uses three exercise parameters:

Duke prognostic treadmill score = Exercise time (minutes based on the Bruce protocol) - (5 x maximum ST segment deviation in mm) - (4 x exercise angina [0=none, 1=nonlimiting, and 2=exercise limiting]).

Patients are classified as low, moderate, or high risk according to the score: Low-risk-score ≥+5, Moderate-risk-score from -10 to +4, and High-risk-score <-11.

Given that asymptomatic patients were excluded from these studies there are no data applying the results of the Duke treadmill score to asymptomatic patients who are screened for CAD. In addition, even among symptomatic patients, the score has limited prognostic utility in patients ≥75 years of age (Kwok, 2002). The 2002 ACC/AHA guidelines suggested that exercise radionuclide myocardial perfusion imaging or exercise echocardiography has

potential use as a second test in asymptomatic patients who have an intermediate or high risk Duke treadmill score on exercise ECG testing even though the score has not been evaluated in asymptomatic patients (ACC/AHA 2002).

3. Treadmill exercise ecg testing

Also known as an exercise tolerance test, it is essential in evaluating for diagnosis and prognosis of coronary artery disease, as well as assessment of functional capacity or tolerance. Exercise ECG testing is the most commonly used noninvasive test because it is simple and inexpensive

Absolute
Acute myocardial infarction (within two days)
Unstable angina
Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
Symptomatic severe aortic stenosis
Uncontrolled symptomatic heart failure
Acute pulmonary embolus or pulmonary infarction
Acute myocarditis or pericarditis
Active endocarditis
Acute aortic dissection
Acute noncardiac disorder that may affect exercise performance or be aggravated by exercise (eg, infection, renal failure, thyrotoxicosis)
Inability to obtain consent
Relative*
Left main coronary stenosis or its equivalent
Moderate stenotic valvular heart disease
Electrolyte abnormalities
Severe hypertension (systolic ≥200 mmHg and/or diastolic ≥110 mmHg)
Tachyarrhythmias or bradyarrhythmias, including atrial fibrillation with uncontrolled ventricular rate
Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
Mental or physical impairment leading to inability to cooperate
High-degree atrioventricular block

Table 1. Absolute and Relative contraindications to Exercise ECG testing

The most common groups of patients that are excluded from exercise ECG testing are those patients unable to exercise sufficiently to reach 85% of maximum predicted heart rate (MPHR) and those with ECG changes at rest that can interfere with interpretation of the test. The exercise ECG cannot be interpreted in the presence of resting ST segment changes, left ventricular hypertrophy, left bundle branch block, a ventricular paced rhythm, or the Wolff Parkinson White syndrome. The patient must also be able to exercise adequately, since failure to achieve at least 85 percent of the predicted maximal heart rate is considered inadequate to rule out ischemic heart disease if the test is otherwise negative.

Achieving 85% of MPHR is the universally-accepted threshold that guarantees an adequate level of stress (ACC/AHA 2002). Some patients attain that level within the first couple of minutes on the treadmill, which is a sign of deconditioning while others may not get there until they are in the more advanced stages of the test suggesting either chronotropic

ACC/AHA guideline summary: Exercise ECG testing without an imaging modality for the diagnosis of obstructive coronary heart disease (CHD)

Class I - There is evidence and/or general agreement that exercise ECG testing for the diagnosis of CHD is indicated in patients with:

- An intermediate pretest probability of CHD based upon age, gender, and symptoms, including patients with complete right bundle branch block or less than 1 mm ST depression, in the absence of the exceptions listed in class IIb and class III.

Class IIa - The weight of evidence or opinion is in favor of the usefulness of exercise ECG testing for the diagnosis of CHD in patients with:

- Suspected variant (vasospastic) angina.

Class IIb - The usefulness of exercise ECG testing for the diagnosis of CHD is less well established in patients with:

- A high or low pretest probability of CHD.
- Digoxin therapy and less then 1 mm of ST segment depression at baseline.
- Electrocardiographic evidence of left ventricular hypertrophy and and less then 1 mm of ST segment depression at baseline.

Class III - There is evidence and/or general agreement that exercise testing for risk assessment and prognosis in patients at intermediate or high probability of CHD is not useful in the following settings:

- Patients with the following baseline ECG abnormalities:
  1. Preexcitation (Wolff-Parkinson-White) syndrome.
  2. Electronically paced ventricular rhythm.
  3. More than 1 mm of ST segment depression at rest.
  4. Complete left bundle branch block.
- An established diagnosis of CHD due to prior myocardial infarction or coronary angiography. However, testing may be warranted in such patients to assess functional capacity and prognosis.

Data from Gibbons, RJ, Abrams, J, Chatterjee, K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina--summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Circulation 2003; 107:149.

Table 2.

incompetence or an extremely conditioned athlete. Chronotropic incompetence can be a manifestation of coronary artery disease (Sugumaran, 2010). Another prognostic factor for CAD is the amount of ST segment depression that occurs during or immediately after exercise. In general, these ECG changes have a sensitivity of 50 to 70% and a specificity of 60 to 80%.

In general, exercise ECG testing provides more information than pharmacologic stress for the following reasons: exercise documents the workload that induces ischemia, exercise capacity and hemodynamic responses are predictors of prognosis independent of ischemia as stated above and ischemia at a low workload indicates a greater likelihood of severe disease and a worse prognosis than does the same degree of ischemia at a high workload. Furthermore, the inability to exercise, without having mechanical limitations, is itself associated with increased cardiovascular risk.

The main disadvantages are that the sensitivity is lower than that of stress imaging techniques, the poor specificity with marked ST-T abnormalities on resting ECG, with digoxin use, with left bundle branch block (LBBB) pattern or pacemakers, or in female population, and it does not accurately localize the site or extent of myocardial ischemia, which is important in patients who have undergone revascularization (ACC/AHA 2002).

4. Characteristics of myocardial perfusion agents

Radionuclide myocardial perfusion imaging (MPI) involves the visualization of a radiopharmaceutical that is distributed throughout the myocardium in proportion to coronary blood flow, thereby permitting the determination of relative blood flow in various regions of the heart. Perfusion imaging is dependent upon the physical properties of the radiolabeled tracer, its delivery, and its extraction and retention by the myocyte. Both cell membrane integrity and energy utilization are necessary for intracellular extraction and retention of tracer. Thus, retained tracer activity is synonymous with myocyte viability. Revascularization of such segments can lead to improvement in left ventricular function. The ideal perfusion agent would have the following characteristics: high first pass

myocardial extraction, linear relationship between uptake and flow, uptake independent of metabolic state, and a stable distribution during imaging.

4.1 Thallium-201

Thallium-201 (Tl-201) is a radioactive element that is similar to potassium analogs first used in perfusion imaging, but with superior imaging characteristics. It is cyclotron produced, and therefore requires off-site manufacturing. The principal photopeaks are gamma rays at 135 keV (2.7 percent) and 167 keV (10 percent), and mercury X-rays of 69 to 83 keV (85-90 %) (Lebowitz, 1975). The physical half-life of thallium-201 is prolonged (73 hours), limiting the overall amount that can be administered to 2 to 4 mCi. Thallium uptake is partly an active process involving the Na-K-ATPase pump. Due to the relatively small contribution of active transport, extraction and uptake of thallium is relatively unaffected by ischemia, hypoxia, or digoxin and is directly proportional to coronary blood flow (Strauss, 1975).

Following thallium's initial extraction, there is a continuous exchange between the myocyte and the extracellular compartment, resulting in a phenomenon called redistribution. Intake of thallium into the cell continues via additional extraction of thallium that still remains in the blood and recirculation of tracer that has already been washed out of the intracellular compartment. Thallium may leak out of various regions within the myocardium at different rates, based upon coronary blood flow. Thus, an area that has higher coronary flow may permit the egress of thallium at a faster rate than a region of low flow, demonstrating a "differential washout" of thallium.

Redistribution often begins as early as 20 minutes following thallium administration and may result in the partial or total resolution of perfusion defects noted shortly after stress imaging. Thus, post-stress imaging should begin within 15 minutes after the initial injection. However, the estimate of perfusion is different at three to four hours after thallium delivery than under true resting conditions, and can overestimate the extent of myocardial necrosis. This potential limitation may be overcome by a second injection of a smaller dose of thallium immediately following the redistribution images. Thallium redistribution can be affected by several factors such as changes in coronary blood flow the administration of nitrates, and consequently the recognition of reversible myocardial ischemia (Medrano, 1993).

Reverse redistribution is a finding in which the perfusion defect appears worse on the delayed redistribution perfusion images (three to four hours after thallium injection) than on the initial images. This phenomenon is thought to be related to hyperemic blood flow that causes enhanced uptake of thallium on initial post-stress images, and a more rapid clearance of thallium, producing the appearance of a perfusion abnormality (Weiss, 1986). Reverse redistribution is consistent with viable myocardium. However, its presence in a patient with a low likelihood of ischemia and without other evidence of ischemia is felt to represent an artifact.

Imaging Protocols. A single dose of 2.5-4.0 mCi of Tl-201 is injected prior to peak exercise stress or at peak pharmacologic vasodilatation, and single-photon emission computed tomography (SPECT) imaging starts 10-15 minutes later. Redistribution (rest) imaging is

done 2.5-4.0 hours later. In cases where standard stress-redistribution imaging shows a fixed or minimally reversible perfusion abnormality, myocardial viability can be assessed with a rest image at 18-24 hours or following reinjection of an additional 1-2 mCi dose of Tl-201. An alternative method for viability assessment is injection of 3-4 mCi of Tl-201 at rest followed by 3- to 4-hour redistribution imaging (Henzlova, 2009).

Clinical indications	Standard exercise tests	Myocardial nuclear perfusion imaging	Stress echocardiography
Detection of coronary heart disease (sensitivity)	Good (65%)	Very good (85%)	Very good (85%)
Exclusion of coronary heart disease (specificity)	Good (85%)	Very good (90%)	Very good (90%)
Accuracy in presence of marked baseline ST-T abnormalities	Poor	Very good	Very good
Localize myocardial ischemia	Poor	Very good	Good
Assess myocardial viability	Poor	Good	Good
Preoperative evaluation	Limited	Good	Good
Prognosis for CHD or post-MI	Good	Very good	Probably very good (limited studies)
Accuracy for ischemia with regional wall motion abnormalities	---	Very good	Good
Evaluation of chest pain syndromes (resting studies)	---	Good	Probably good
Infarct quantification (resting studies)	---	Good	Modest
Cost	Relatively cheap	Expensive	Modest

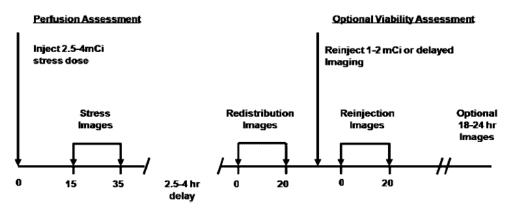Table 3. Efficacy of the different methods of stress testing in specific clinical settings

Fig. 1. Stress/redistribution/reinjection/18- to 24-hour Tl-201 imaging protocol.
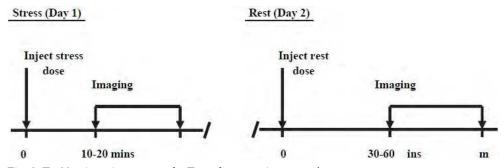

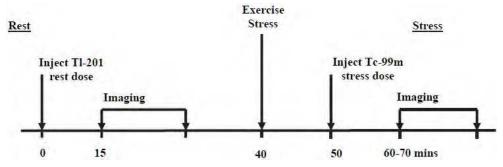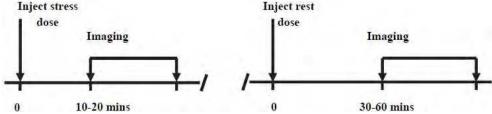Fig. 2. Tc-99m imaging protocols: Two-day exercise stress/rest.

Fig. 3. Rest Tl-201/stress Tc-99m separate-acquisition dual-isotope protocol.

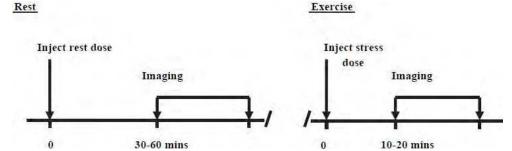Fig. 4. Tc-99m imaging protocols: One-day exercise stress/rest.

Fig. 5. Tc-99m imaging protocols: One-day rest/exercise stress.

In summary, thallium-201 has the following advantages: myocardial uptake is proportional to flow, redistribution allows a single injection for both stress and rest images The two primary disadvantages are its low photon energy resulting in more scatter and soft tissue attenuation and the longer physical half-life limiting the allowable dose which reduces image quality.

4.2 Technetium-99 labeled agents

There are several physical advantages for the use of technetium-99m (Tc-99m) perfusion tracers. The higher photon energy (140 keV) is well suited for gamma camera imaging, and

may result in less photon attenuation and scatter due to soft tissue when compared with thallium-201. A half-life of six hours and favorable dosimetry permits the administration of substantially more activity, thereby resulting in a high number of emitted photons and improved image resolution. The increased photon flux also permits functional imaging with gated SPECT or first-pass techniques. Tc-99m is a generator produced product, and the workhorse of most nuclear medicine departments. As a result, it is readily available at most institutions. Three 99m Tc-labeled myocardial perfusion agents are now available in clinical practice: sestamibi, tetrofosmin, and teboroxime but only the first two are commonly used. Other tracers are in various stages of development. Each compound has unique properties that make it suitable for certain types of imaging

Clinical indications	Standard exercise tests	Myocardial nuclear perfusion imaging	Stress echocardiography
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Exclusion of coronary heart disease (specificity)	Good (85%)	Very good (90%)	Very good (90%)
Accuracy in presence of marked baseline ST-T abnormalities	Poor	Very good	Very good
Localize myocardial ischemia	Poor	Very good	Good
Assess myocardial viability	Poor	Good	Good
Preoperative evaluation	Limited	Good	Good
Prognosis for CHD or post-MI	Good	Very good	Probably very good (limited studies)
Accuracy for ischemia with regional wall motion abnormalities	---	Very good	Good
Evaluation of chest pain syndromes (resting studies)	---	Good	Probably good
Infarct quantification (resting studies)	---	Good	Modest
Cost	Relatively cheap	Expensive	Modest

Table 4. Efficacy of the different methods of stress testing in specific clinical settings

Sestamibi Tc-99m (Cardiolite™) is in a class of compounds known as isonitriles. Sestamibi has the following general characteristics: it is a lipophilic monovalent cation with transient hepatic uptake, minimal lung uptake, and a good target-to-background ratio unlike thallium uptake. Sestamibi uptake is not dependent upon the Na-K-ATPase pump. Distribution within the myocardium is proportional to blood flow (Wackers, 1989).

Due to minimal redistribution over time, Sestamibi is well suited to the prolonged acquisition times associated with tomographic imaging. The absence of significant sestamibi redistribution necessitates two separate injections of the radiopharmaceutical, one during peak stress and a second while at rest. The lack of sestamibi redistribution permits greater flexibility in scheduling, since imaging is not mandated immediately after injection. Sestamibi can be used to quantify the area of risk in a patient suffering an acute myocardial infarction. Since sestamibi activity reflects myocardial perfusion at the time of injection, defects on these early images indicate possible areas of jeopardized myocardium.

Sestamibi can be given to patients with chest pain and nondiagnostic findings on ECG, and images taken later, even after treatment of the chest pain. Both gated SPECT and first pass imaging have been performed successfully with this agent. This evaluation may be one of the most valuable clinical attributes of sestamibi scintigraphy (DePuey, 1995).

In summary, Tc-99m sestamibi has the following advantages: myocardial uptake is proportional to flow, there is stable retention of tracer (minimal redistribution), and simultaneous perfusion and function assessment is possible

Pharmacologic test	Sensitivity, percent	Specificity, percent
Adenosine echocardiography	72	91
Adenosine SPECT MPI	90	75
Dipyridamole echocardiography	70	93
Dipyridamole SPECT MPI	89	65
Dobutamine echocardiography*	80	84
Dobutamine SPECT MPI	82	75

Table 5. Weighted mean sensitivities and specificities of pharmacologic stress tests.

Tetrofosmin (Myoview™) is a lipophilic, cationic diphosphine compound. It has good myocardial uptake with rapid clearance from the liver, lungs, and blood (Higley, 1993). As with sestamibi, there is little myocardial washout over time. Thus, high quality myocardial images can be obtained from five minutes to several hours after injection. The more rapid clearance from the liver with tetrofosmin may lead to less artifact from subdiaphragmatic activity, which is a common problem with Tc-99m sestamibi (Zaret, 1995).

Exercise tetrofosmin imaging is of prognostic value in patients with coronary heart disease, adding incremental information to that provided by clinical and exercise data. In a multicenter review of 4278 patients, the mortality rate in those with a normal exercise or adenosine tetrofosmin SPECT study was 0.6 percent per year, similar to published rates for normal thallium and sestamibi studies (Shaw, 2003).

In summary, important features of Tc-99m tetrofosmin include: myocardial uptake is proportional to flow, minimal redistribution occurs, and there may be more rapid washout from the liver than with sestamibi, permitting earlier imaging after injection.

Teboroxime (Cardiotec™) is a neutral, lipophilic perfusion agent in a class of compounds called the boronic acid adducts of technetium dioxime. Teboroxime differs from thallium and sestamibi in that its uptake appears to be relatively insensitive to myocardial injury. As a result, teboroxime may serve as a pure blood flow agent that is not dependent upon cellular viability (Heller,1996). In contrast to sestamibi, teboroxime is characterized by rapid uptake and washout, with a clearance half-time in the myocardium of only a few minutes.

Teboroxime appears to be a more accurate marker of flow than the other tracers at high flow rates, and may prove useful for quantification of coronary blood flow. The washout of teboroxime from the myocardium is rapid and flow-dependent. The short myocardial residence time of teboroxime necessitates rapid patient positioning and image acquisition, which increases the difficulty of testing. In addition, the lower count rates with such rapid imaging protocols preclude the use of gated SPECT imaging. In summary, the important features of Tc-99m teboroxime are that it is the most accurate marker of flow among single photon agents its rapid myocardial washout limits its clinical utility.

NOET is a neutral lipophilic compound with a technetium-nitrido (Tc(N)) core. Preliminary studies indicate that NOET may undergo redistribution similar to Tl-201. This property would make it attractive for myocardial perfusion studies, since it would have the clinically useful properties of Tl-201 and the more favorable imaging characteristics of Tc-99m. Small studies have demonstrated comparable accuracy to Tl-201 for the detection of coronary artery disease (Jeetley, 1995).

5. Exercise radionuclide myocardial perfusion imaging (rMPI)

SPECT imaging is performed by using a gamma camera to acquire multiple 2-D images from multiple angles. A computer performs a tomographic reconstruction algorithm to the multiple projections, yielding a 3-D dataset. Cardiac gated acquisitions are possible with SPECT, which are thereby used to obtain quantitative information about myocardial perfusion, thickness, and contractility of the myocardium during various parts of the cardiac cycle, and also to allow calculation of left ventricular ejection fraction, stroke volume, and cardiac output.

Exercise rMPI is a valuable tool for the evaluation of selected patients with known or suspected CAD. The development of 99m-Tc-labeled agents with improved imaging characteristics and ECG gated acquisition permits simultaneous assessment of myocardial perfusion and left ventricular systolic function. This in turn translates into superior diagnostic accuracy and provides important prognostic information regarding cardiac events. rMPI depicts the distribution of blood flow in the myocardium by imaging the uptake of an intravenously administered radionuclide. Abnormal uptake of a radionuclide results in a "cold spot" on the image localizing areas of relatively reduced myocardial blood flow associated with ischemia or scar. The relative regional perfusion distribution can be assessed at rest, during cardiovascular stress, or both (Strauss, 2008). The differentiation of ischemic myocardium is made by comparing images obtained at the peak of maximal exercise or during pharmacological stress with those obtained at rest. During stress, blood flow increases in normal coronary arteries. Because myocardial uptake of the radionuclide tracer is proportional to coronary blood flow, MPI radiotracer intensity is diminished in areas of hypoperfusion.

The choice among the different types of stress tests is based upon the patient's ability to exercise to a level high enough to produce meaningful results on exercise ECG testing, the possible presence of baseline electrocardiographic abnormalities that could interfere with the interpretation of exercise ECG testing, and whether or not it is important to localize ischemia or assess myocardial viability
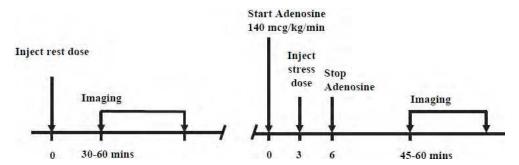

Fig. 6. Tc-99m imaging protocols: One-day rest/adenosine pharmacologic stress.

The 2002 ACC/AHA guidelines on chronic stable angina and on exercise testing published recommendations for the use of stress imaging as the initial test for diagnosis or for risk assessment in patients. Exercise rMPI is an option for diagnosis in patients with an intermediate pretest risk of CHD who are able to exercise but have baseline ECG abnormalities that can interfere with exercise ECG testing.
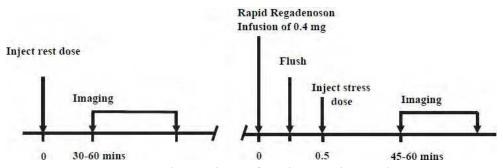
Fig. 7. Tc-99m imaging protocols: One-day rest/regadenoson pharmacologic stress.
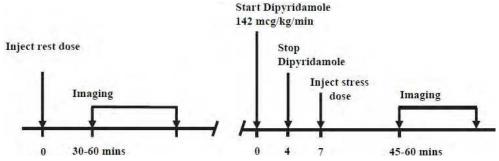

Fig. 8. Tc-99m imaging protocols: One-day rest/dipyridamole pharmacologic stress.

Patients with non-diagnostic or equivocal stress echo that were tested for ischemic symptoms would qualify for a PET scan.
Patients with non-diagnostic or equivocal nuclear testing that are being assessed for ischemic symptoms qualify for a PET scan.
Patients that can not exercise and need pharmacologic testing that have ischemic symptoms or need clearance for major surgery would qualify for a PET scan.
Patients with BMI over 40 and in some cases over 35, which are being assessed for ischemic symptoms, can go straight to a PET scan.
Patients with breast implants or large pendulous breasts, undergoing assessment for ischemic symptoms, can undergo PET imaging.
Patients with a high CAC, viewed as over 300 or 400, can often go to PET imaging. Symptoms are needed to pre-certify.
Patients with a Coronary CTA showing borderline obstructive plaque, usually in the 50-70% range, can go directly to PET imaging. Again, symptoms make it easier.
Patients with new findings of CHF and/or a cardiomyopathy can usually proceed directly to PET testing.
Patients requiring a decision regarding the need for revascularization, either from the ischemic or viability standpoint.

Table 6. Clinical Recommendations for Appropriate PET Testing

	Adenosine*	Dipyridamole*	Dobutamine
Number of Peripheral IV lines recommended	2	1	2
Radiotracer Injection	Mid infusion	3 minutes after completion of infusion	When target heart rate is reached

Table 7.

A normal exercise rMPI is associated with a low risk for future cardiac events (<1 percent annual mortality rate). In contrast, the presence of high-risk findings, such as extensive ischemia, reversible ischemia in multiple segments, transient or persistent cavity dilatation, or a left ventricular ejection fraction of <45 percent, predict an annual mortality rate above 3 percent. In the study just cited, the annual rate of cardiac death in patients with mildly

abnormal, moderately abnormal, or severely abnormal perfusion defects was 2.7, 2.9, and 4.2 percent, respectively (Hachamovitch, 1998). High-risk patients should undergo coronary angiography.

Tl-201 Protocol	Stress (mCi)	Rest (mCi)	Reinjection (mCi)
Stress/Rest	2.5–4.0	-	-
Stress/Rest/Reinjection	2.5–4.0	-	1.0–2.0
Viability Only	-	3.0–4.0	-

Tc-99m Protocol	Stress (mCi)	Rest (mCi)
Two day	24–36	24–36
One day, Stress/Rest	8–12	24–36
One day, Rest/Stress	24–36	8–12
Dual isotope	24–36	2.5–4.0

Table 8. Suggested radiopharmaceutical doses for myocardial perfusion imaging protocols

	Thallium-201	Technetium-99m
Dose	2-4 mCi	20-30 mCi
Photon energy	69-83 keV	140 keV
Half-life	73 hours	6 hours
Availability	Cyclotron-produced	Generator produced; often available on site
Significant redistribution	Yes	No

Table 9. Comparison of Thallium-201 and Tecnetium-99m

6. Pharmacologic stress testing with either dipyridamole, adenosine, or regadenoson

Exercise is the preferred method of stress in SPECT rMPI. As stated earlier, patients must be able to exercise to 85% of their MPHR or 5 METs. However, there are many patients whom are unable to exercise due to physical impairments or deconditioning. When this occurs, pharmacologic stress agents are used in place of exercise. Pharmacologic stress agents are classified as either vasodilator or inotropic/chronotropic drugs. Adenosine, regadenoson, and dipyridamole produce coronary vasodilation in the presence of significant coronary stenosis; they induce heterogeneous myocardial blood flow due to differences in coronary flow reserve. The heterogeneity of myocardial blood flow during hyperemia is detectable with a perfusion tracer and SPECT or PET imaging. In patients who are unable to exercise and have contraindications to vasodilators, dobutamine is currently recommended as the stress agent in conjunction with either echocardiography or rMPI.

Adenosine (Adenoscan ™) is the most widely used pharmacologic stress agent in the United States, currently accounting for approximately 44% of pharmacologic stress MPI procedures (Malvern, 2009). It directly activates cell-surface A1 and A2 adenosine receptors in the coronary arteries, resulting in a 3.5-to 4-fold increase in myocardial blood flow (Henzlova, 2009). It is administered through a pump infusion at a weight-based dosage of 140 ug/kg/min over 6 minutes, for a total dose of 0.84 mg/kg. The radiotracer is injected at the midpoint of the infusion, depending on a 4 or 6 minute protocol. The addition of

	Thallium	Sestamibi	Tetrofosmin	Teboroxime
Class	Element	Isonitrite	Diphospine	BATO
Charge	Positive	Positive	Positive	Neutral
Lipophilic	No	No	No	Yes
Extraction	Mod-high	Moderate	Moderate	High
Retention	Moderate	High	High	Low
Redistribution	Yes	Minimal	Minimum	Yes
Start time*	<15 min	15-60 min	15-30 min	<3 min
Imaging protocol	1 day	1 or 2 days	1 or 2 days	1 day
Gated SPECT	Possible	Yes	Yes	No
First pass	No	Yes	Yes	No
Viability assessment	Yes	Yes	Yes?	No

Table 10. Characteristics of various myocardial perfusion agents

exercise (walking on the treadmill at 0% incline at 1 mi/hr) has been shown to improve the detection of ischemia as well as scan quality (Holly, 2003). Adenosine is contraindicated in patients who have second-or-third degree atrioventricular (AV) block or sinus node disease (except those with a functioning artificial pacemaker), and in patients with known or suspected bronchoconstrictive or bronchospastic lung disease, such as asthma or chronic obstructive pulmonary disease. Based on clinical trial, the most common side effects associated with adenosine were flushing (44%), chest discomfort (40%), and dyspnea (28%). These side effects are very transient lasting up to a minute and usually resolve by the end of the infusion. If necessary, to reverse these effects one may administer aminophylline 50 to 250 mg by slow intravenous injection (50-100 mg over 30-60 seconds).

Intravenous dipyridamole was the first agent approved for pharmacologic stress in MPI, in 1990, and is currently being used in roughly 26% of pharmacologic stress MPI procedures in the United States (Malvern, 2009). It induces coronary vasodilation by inhibiting the intracellular reuptake of endogenous adenosine. It is administered via pump infusion at a rate of 0.142 mg/kg/min over 4 minutes, for a total dose of 0.57 mg/kg. It is contraindicated only in patients with hypersensitivity to it, but is generally considered to be contraindicated with bronchoconstrictive or bronchospastic lung disease as well (Henzlova, 2008). The most common side effects are: chest pain (20%), headache (12%), and dizziness (12%). Similar to adenosine, aminophylline can be used to reverse the above side effects.

In April 2008, regadenoson (Lexiscan ™) was the first selective A2A adenosine receptor agonist to be approved for use in rMPI, and currently accounts for 24% of pharmacologic stress MPI procedures (Malvern, 2009). The selectivity of A2Aadenosine receptor agonists greatly reduce or even eliminate the side effects associated with the adenosine or dypyrimadole. It is administered as a rapid injection, over approximately 10 seconds. It is contraindicated in patients with sick sinus syndrome, high degree AV block, and in patients receiving oral dipyridamole therapy.

Both SPECT and positron emission tomography (PET) imaging provide useful diagnostic and prognostic information during pharmacologic stress test. However, PET is preferable in patients with prior equivocal SPECT results and, possibly, in patients with obesity or established CAD.

7. Stress echocardiography

Exercise or pharmacologic stress two-dimensional (2D) trans-thoracic echocardiography may also be used to suspect coronary artery disease by demonstrating inducible wall motion abnormalities, to assess myocardial viability prior to coronary revascularization, to risk stratify patients with known or suspected CAD, and to risk stratify patients prior to non-cardiac surgery. The high specificity of stress echocardiography compared to other modalities contributes to its utility as a cost-effective diagnostic method. The sensitivity and specificity are 76 and 88 percent respectively (Fleischmann, 1998). There are several advantages of stress echocardiography over stress rMPI, including lower cost, shorter patient time commitment, and avoidance of radiation exposure. The latter is an important issue to consider as patients often have multiple stress imaging tests during their lifetime.

Among patients who are able to exercise, exercise rMPI or exercise echocardiography can be used to identify the extent, severity, and location of ischemia in patients with an intermediate pretest probability of disease who do not have left bundle branch block or a paced ventricular rhythm but have other resting ECG abnormalities that could interfere with the interpretation of exercise ECG testing. Both may be used in patients with prior revascularization and to assess the functional significance of coronary lesions, if not already known, prior to percutaneous coronary intervention.

Exercise echocardiography or exercise rMPI is primarily recommended as the initial stress test in patients who can exercise but have baseline ECG abnormalities (i.e. LVH, ST-T changes, LBBB) that interfere with interpretation of exercise ECG testing.

In three reviews, exercise echocardiography (compared to coronary angiography) had a sensitivity of 79 to 85 percent and a specificity of 72 to 87 percent for the diagnosis of coronary artery disease (Fleischmann, 1998) (Kim, 2001) (Arruda, 2001). False negative results are more likely with sub-maximal exercise, single vessel disease, and moderate (50 to 70 percent) stenoses (Marwick, 1992).

When treadmill exercise stress is used, images are obtained immediately after exercise since imaging during exercise is not feasible. A potential limitation with this approach is that ischemia may resolve rapidly after discontinuing the exercise and a wall motion abnormality that developed during peak exercise may rapidly reverse to normal after the test is stopped. Thus, images need to be acquired as rapidly as possible (within 60 to 90 seconds after cessation of exercise). This method requires that the patient move from the treadmill into a recumbent position for imaging within a few seconds so that images can be obtained within 60 seconds after peak exercise. Due to tachypnea and tachycardia that develop at peak exercise, the heart is frequently visible for only one or two beats at end expiration. Early image acquisition is necessary since ischemia induced wall motion abnormalities may resolve rapidly as the heart rate slows, causing a decrease in the sensitivity of the test, especially for single vessel disease. Failure to achieve or exceed target heart rate also decreases sensitivity.

Some laboratories perform stress echocardiography using supine or upright bicycle ergometry. The peak heart rate and achieved double product (the product of peak heart rate and peak systolic blood pressure) are usually lower and the achieved blood pressure is higher after a bicycle protocol than a treadmill test. A typical supine bicycle protocol

increases the workload by 25 W every three minutes until an endpoint is achieved. In this protocol, an exercise duration of 20 minutes is typical for a healthy adult without endurance training. The protocol can be modified during image acquisition to allow complete data collection without increasing the workload once maximum capacity is reached.

A major advantage of bicycle ergometry is that it allows continuous monitoring of wall motion during exercise. More importantly, imaging throughout the study (so that rest, intermediate, peak and recovery images are obtained) may permit detection of the onset and disappearance of transient wall motion abnormalities and improve sensitivity of detection of coronary artery disease (Park, 2007). An additional advantage of continuous imaging is that during low level stress, an improvement in a dysfunctional wall is equivalent to improvement with low dose dobutamine; therefore, a segment that improves during low level exercise has a high likelihood of viability. If segmental wall motion deteriorates beyond its resting level of dysfunction at peak stress, then the affected segment has a high likelihood of being supplied by stenosed coronary artery.

	Dipyridamole	Adenosine	Regadenoson	Dobutamine
Chemical	Pyrimidine derivative	Endogenous vasodilator of purine derivative	Purine derivative	Synthetic catecholamine
Onset and duration of action, half-life	Effect peaks at 7-15 minutes, half-life 30-45 minutes	Immediate onset, half-life less than five seconds, effects disappear rapidly after infusion	Peak 1-4 minutes after injection Half-life of ≈30 minutes	Onset 1-2 minutes, half-life 2 minutes
Mechanism of action	Blocks reuptake of endogenous adenosine causing coronary vasodilation	Stimulation of adenosine receptor A2A causing coronary vasodilation	Stimulates A2A adenosine receptor causes coronary vasodilation	Alpha-1, beta-1, and beta-2 stimulation increases myocardial O2 demand and secondary vasodilatation
Dose	140 µg/kg per min for 4 minutes (maximum 0.56 mg/kg)	140 µg/kg per min for 4-6 minutes	Regadenoson 0.4 mg/5 mL	5-40 µg/kg per min, depending upon heart rate response
Radionuclide injection	7-9 minutes after initiation of infusion	3 minutes into infusion; infusion continued for further 1-3 minutes	10-20 seconds after regadenoson	At peak stress
Hemodynamics	Slight increase in heart rate and slight decrease in blood pressure (BP)	Slight increase in heart rate and slight decrease in BP (adenosine more than dipyridamole)	Slight increase in heart rate and slight decrease in BP	Target heart rate 85 percent of maximum predicted heart rate
Side effects	Occur frequently, but minor	Same as dipyridamole but resolve rapidly; heart block more common	Dyspnea, headache and flushing	Most common chest pain, most serious nonsustained ventricular tachycardia, nonfatal myocardial infarction
Contraindications	Bronchospasm, second or third degree AV block or sick sinus syndrome (unless protected by a functioning pacemaker)	Same as dipyridamole	Second- or third-degree AV block or sinus node dysfunction Caution for bronchospasm	Recent acute coronary syndrome, hemodynamic and electrophysiologic instability

Table 11. Comparisons between different pharmacologic stress agents.

When exercise echocardiography is performed during supine or upright bicycle exercise, images are obtained during exercise so ischemic dysfunction is more likely to be captured if adequate workloads are attained. Continuous echocardiographic monitoring has another potential advantage in that it permits detection of the biphasic response of dysfunctional yet viable myocardium that is characterized by initial improvement of regional function followed by deterioration similar to the biphasic response detected during dobutamine stress echocardiography.

Dobutamine increases heart rate and myocardial contractility. The onset of action is within one to two minutes of intravenous infusion, the half-life is two minutes, and the drug is metabolized via methylation and conjugation. At a dose of 20 µg/kg per min, there is a small but significant increase in systolic blood pressure (mean 12 mmHg in one report) and at 40 µg/kg per min, the mean heart rate is 120 to 125 beats/min.

The 2007 ACC/AHA perioperative guidelines regarding stress testing in patients with left bundle branch block concluded that exercise imaging (with either echocardiography or

rMPI) was suboptimal (due to low specificity) and that either vasodilator rMPI or dobutamine stress echocardiography is preferred for these patients (Fleisher, 2009).

The standard dobutamine stress test components are: graded dobutamine infusion in five three-minute stages starting at 5 μg/kg/min, followed by 10, 20, 30, and 40 μg/kg/min. An initial dose of 2.5 μg/kg/min is sometimes employed in tests evaluating viability. Low-dose stages facilitate recognition of viability and ischemia in segments with abnormal function at rest, even when viability evaluation is not the main aim of the test (Pellikka, 2007). End points are achievement of target heart rate (defined as 85 percent of age MPHR), new or worsening wall-motion abnormalities of moderate degree, significant arrhythmias, hypotension, severe hypertension, and intolerable symptoms. Atropine, in divided doses of 0.5 mg to a total of 2.0 mg, should be administered as needed to achieve target heart rate. Atropine increases the sensitivity of dobutamine echocardiography in patients receiving beta-blockers and in those with single-vessel disease (McNeill,1992).

8. Cardiac Computed Tomography Angiography (CCTA) and stress Cardiac Magnetic Resonance Imaging (CMRI)

Cardiac computed tomography angiography (CCTA) is an imaging method that uses a computed tomography (CT) scanner to look at the structures and blood vessels of the heart. In some situations a CCTA can be done instead of, or in addition to, a stress test. Both CCTA and a stress test may be used to screen patients for CAD.

Calcium scoring and CCTA have different clinical indications. Calcium scoring is primarily used for risk stratification of asymptomatic patients, while CCTA is primarily used in patients with acute or chronic chest pain. One potential use of performing a non-enhanced calcium scoring study before a CCTA is to decide whether to proceed with CCTA in patients with extensive coronary calcium. There is no established calcium score cutoff value above which CCTA will not be diagnostic, but a score of 1000 is often used. In the multicenter Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography (ACCURACY) trial, the specificity of CCTA was significantly reduced (from 86% to 53%) in patients with calcium scores greater than 400 (Budoff, 2008).

A 2008 scientific statement from the AHA indicates that the potential benefit of noninvasive coronary angiography is likely to be the greatest for symptomatic patients who are at intermediate risk for CAD after initial risk stratification, including patients with equivocal stress tests. CCTA is recommended over coronary magnetic resonance angiography (MRA) because of superior diagnostic accuracy. Neither coronary CCTA nor MRA is recommended to screen for CAD in patients who have no signs or symptoms suggestive of CAD.

The following indications were rated as appropriate for coronary CT angiography (Hendel, 2006): evaluation of chest pain syndrome in patients with intermediate pretest probability of CAD and uninterpretable ECG or inability to exercise, evaluation of chest pain syndrome in patients with uninterpretable or equivocal stress test, evaluation of acute chest pain in patients with intermediate pretest probability of CAD and no ECG changes and serial enzymes negative, evaluation of coronary arteries in patients with new-onset heart failure to assess etiology, and evaluation of suspected coronary anomalies.

A CCTA can directly estimate the amount of stenosis likely indicating an area of ischemia CCTA is not recommended in patients with either a very low pretest likelihood of coronary stenosis or a high pretest likelihood of coronary stenosis. Concerns about radiation exposure limit the use of CCTA in patients with very low likelihood of coronary disease. Patients with high likelihood of CAD are likely to require invasive coronary angiography and intervention. The usefulness of CCTA is reduced in patients with pronounced coronary calcification. In a 2008 meta-analysis (Mowatt, 2008), CCTA had a sensitivity of 99% and negative predictive value (NPV) of 100% for patient-based detection of significant CAD. The ACCURACY trial suggested that, compared with other noninvasive modalities such as stress echocardiography and stress nuclear testing, CCTA has comparable specificity but superior sensitivity and NPV.

Along with accurately depicting left and right ventricle ejection fractions, volumes, and myocardial mass, CMRI can also reveal regional wall motion abnormalities in ischemic tissue. By using T2-weighted imaging and assessment of left ventricular wall thickness, CMRI adds a level of specificity that no other stress modality can reach. Late gadolinium enhancement (LGE) or delayed enhancement CMRI is thought to reflect fibrosis and irreversibly damaged myocardium including acute and chronic MI. The possible role of LGE as a risk predictor for subsequent cardiac events was evaluated in a group of 195 patients without known prior MI, but with known or suspected CAD (Kwong, 2006). During an average follow-up of 16 months, patients with LGE on the baseline study had a higher incidence of major adverse cardiovascular endpoints (MACE) compared to those without this finding. In addition, LGE was the strongest multivariable predictor of MACE taking into account traditional clinical, angiographic, and functional variables. CMRI has been evaluated using dobutamine, dipyramidole, adenosine, or regadenoson as pharmacologic stress. The proper role of this diagnostic tool in the evaluation of patients with suspected or known coronary artery disease remains to be determined. Some of the disadvantages are: cost, availability, motion artifact, and observer bias.

CMRI or CCTA is suggested to evaluate suspected or known congenital or acquired coronary anomalies, particularly to establish the proximal course relative to the great vessels of coronary arteries with abnormal origin. CMRI is preferred in these younger patients to avoid radiation exposure and in patients with contraindications to iodinated contrast or beta blockers. In patients with no signs or symptoms suggestive of coronary artery disease, we recommended that neither CCTA nor CMRI should be used to screen for coronary disease. Noninvasive coronary angiography is reasonable for symptomatic patients who are at intermediate risk for coronary artery disease after initial risk stratification, including patients with equivocal stress test results. Diagnostic accuracy currently favors CCTA over CMRI for these patients. In patients with known or suspected congenital or acquired coronary anomalies, we suggest CCTA or CMRI. CMRI is preferred in younger patients given concerns about potential long-term effects of radiation associated with CCTA. In patients with coronary artery bypass grafts in whom it is not possible to selectively engage clinical important grafts during invasive angiography, we suggest CCTA or CMRI for evaluation of coronary artery bypass graft patency. In patients with contraindications to beta blockers or iodinated contrast or with significant renal dysfunction, CMRI is preferred to CCTA. Neither CCTA nor CMRI should be used to screen for coronary disease in patients who have no signs or symptoms suggestive of coronary artery disease.

9. Positron emission computed tomography myocardial perfusion imaging

PET is an established noninvasive method of evaluating myocardial perfusion and viability (Schelbert, 1994). This technique has the advantage of being able to assess perfusion and metabolism simultaneously. PET requires the use of positron-emitting isotopes (such as oxygen-15, carbon-11, nitrogen-13, and fluorine-18), which are incorporated into physiologically active molecules. During ischemia, myocyte metabolism is shifted to glucose from fatty acids. Thus, uptake of a glucose analog, fluorine-18 labeled deoxyglucose (FDG) by myocytes in an area of dysfunctional myocardium indicates metabolic activity and thus, viability. Regional perfusion can be simultaneously assessed with an agent that remains in the vascular space and thus demonstrates the distribution of blood flow (such as N-13 ammonia or Rb-82). As a result, PET imaging has the potential to differentiate between normal, stunned, hibernating, and necrotic myocardium. The presence of enhanced FDG uptake in regions of decreased blood flow defines hibernating myocardium by PET imaging, while a concordant reduction in both metabolism and flow is thought to represent predominantly necrotic myocardium. Regional dysfunction in presence of normal perfusion is indicative of stunning. Myocardial segments with significant reductions in both blood flow and FDG uptake have only a 20 percent chance of functional improvement following revascularization. In comparison, dysfunctional territories deemed to be hibernating by PET have approximately an 80 to 85 percent chance of functional improvement following revascularization (Lucignani, 1992).

PET MPI is indicated for the diagnosis and risk stratification of suspected CAD in patients with an intermediate or high likelihood of CAD and cannot exercise adequately or have a LBBB or paced rhythm on ECG. PET MPI is also indicated for the detection of the co-presence of CAD and for the assessment of resting myocardial perfusion in patients undergoing the assessment of myocardial viability with FDG PET.

Rubidium-82 generators are delivered to the PET center on a monthly basis. Rubidium has a half life of 75 seconds, making pharmacologic imaging necessary. The patient lies comfortably, with their head outside of the scanner, for 30 minutes. Rubidium-82 is used to obtain cardiac PET images before and after dipyridamole, the pharmacologic agent of choice at this time. Aminophylline can be given at the end of the procedure to minimize side effects, which are minimal.

PET methodology utilizes Beta (+) decay of a nucleus resulting in emission of a positron, which rapidly annihilates with an electron, giving off two 511-keV photons that travel opposite each other (180 degrees). Images are produced as the two photons are detected simultaneously in the ring shaped scanner. Spatial resolution is presently in the range of 4-6 mm, making PET superior to conventional nuclear imaging. Temporal resolution is also superior and clinical studies have consistently shown increased sensitivity and specificity with PET compared to conventional nuclear testing.

PET offers additional benefits in comparison to nuclear testing. As mentioned, the total procedure takes 30 minutes compared to 3-4 hours for nuclear testing. Technetium, the primary isotope in conventional nuclear testing, has become difficult to obtain and recently most labs are limited in their ability to test patients. PET using rubidium-82 has less radiation exposure to the patient and staff. Research in molecular and nanotechnology is within years of taking Cardiac PET imaging and its benefits to a new level.

Patients with non-diagnostic or equivocal stress echo that were tested for ischemic symptoms would qualify for a PET scan.
Patients with non-diagnostic or equivocal nuclear testing that are being assessed for ischemic symptoms qualify for a PET scan.
Patients that can not exercise and need pharmacologic testing that have ischemic symptoms or need clearance for major surgery would qualify for a PET scan.
Patients with BMI over 40 and in some cases over 35, which are being assessed for ischemic symptoms, can go straight to a PET scan.
Patients with breast implants or large pendulous breasts, undergoing assessment for ischemic symptoms, can undergo PET imaging.
Patients with a high CAC, viewed as over 300 or 400, can often go to PET imaging. Symptoms are needed to pre-certify.
Patients with a Coronary CTA showing borderline obstructive plaque, usually in the 50-70% range, can go directly to PET imaging. Again, symptoms make it easier.
Patients with new findings of CHF and/or a cardiomyopathy can usually proceed directly to PET testing.
Patients requiring a decision regarding the need for revascularization, either from the ischemic or viability standpoint.

Table 12. Clinical Recommendations for Appropriate PET Testing

Some of the disadvantages of PET include: limited availability, difficult use with exercise stress and lack of experienced/trained staff. Patients who benefit from PET MPI are those who have an equivocal SPECT MPI for diagnosis or risk stratification of known or suspected CAD, require pharmacologic stress imaging, are more prone to attenuation artifacts such as obese patients, female patients, arms down imaging, and finally those who require myocardial viability assessment

Most PET stress scans are performed using pharmacological stress with vasodilator stress being the most common. The radiotracer is injected during peak hyperemia using the same or a separate intravenous line. Exercise stress is feasible but may be cumbersome due to high radiation dose to personnel, coordination with the cyclotron and patient motion.Rubidium-82 (Rb 82) (76-second half-life) is produced by a generator and is the most widely used radiotracer for clinical PET MPI. The Sr-82 generator that produces Rb-82 is replaced every 28 days, reflecting the physical half-life of Sr-82. The use of N-13 ammonia (9.96-minute half-life) is limited to institutions that have a cyclotron on site. The longer half-life permits exercise stress.

10. Stress testing in women and diabetics

Cardiovascular diseases are the most common cause of death and disability in women in the United States (Eaker, 1999). Between the ages of 45 to 64, one in nine women develops symptoms of some form of cardiovascular disease. After age 65, the ratio climbs to one in three women, according to the National Center for Health Statistics (Mosca, 1997). Women are more likely to initially present with chest pain than a more clearly defined event such as a myocardial infarction. Women rated their chest pain as more intense, used different terms to describe the pain such as sharp or burning, had more symptoms unrelated to pain, and more frequently had pain and other sensations in the neck and throat. Women present about 10 years later than men and with a greater risk-factor burden. Women are less likely than men to have typical angina and those who present to the emergency department with new onset chest pain are approached and diagnosed less aggressively than men. The symptoms of MI in women may differ slightly from those in men. Many cases of myocardial infarction MI in women go unrecognized, particularly at younger ages or in patients with diabetes.

The symptoms of AMI in women differ from those in men, which may in part explain the greater delays in both seeking and receiving care. Women who present with episodic chest pain need to be evaluated for CAD. The likelihood of CAD is based in part upon the character of the presenting symptoms and the presence or absence of coronary risk factors.

The risk assessment must be sex specific because the risk factors themselves, as well as their relative importance, may differ between women and men. In particular, hormonal status, diabetes, smoking, and a family history of premature CAD appear to be more important in women. Women with chest pain, compared to men, have a lower rate of CAD and a higher rate of false positive results on exercise ECG testing (Diamond, 1979).

The process of establishing the diagnosis of CAD in women is similar to that in men, but several points need to be kept in mind: treadmill exercise testing has a higher false-positive rate in women, while stress imaging appears to have similar accuracy. The prevalence of significant coronary disease found at the time of angiography is lower in women than men presenting with chest pain. Women with chest pain and no evidence of atherosclerotic coronary artery disease on coronary angiography may have cardiac syndrome X or microvascular disease, or far more rarely, takotsubo cardiomyopathy or spontaneous coronary artery dissection.

Compared to individuals without diabetes, those with diabetes have a higher prevalence of CAD, a greater extent of myocardial ischemia, and are more likely to have an AMI and silent myocardial ischemia (Hammoud, 2000). The increase in cardiovascular risk is due both to diabetes and to the frequent presence of other risk factors such as hyperlipidemia and hypertension. In addition to the increase in cardiovascular events, patients with type 2 diabetes also have a high rate of asymptomatic coronary artery disease compared to the general population. Furthermore, asymptomatic patients may have coronary anatomy that does not permit optimal outcomes with percutaneous coronary intervention or coronary artery bypass graft surgery. Some diabetic patients have a blunted appreciation of ischemic pain, which may result in atypical anginal symptoms, silent ischemia, or even silent infarction. Silent ischemia in diabetes is thought to be caused at least in part by autonomic denervation of the heart.

Diabetic patients have an increased frequency of silent ST segment depression and coronary perfusion abnormalities during stress testing (Scognamiglio, 2006). Since type 2 diabetes is considered to be a CAD equivalent, the primary purpose of screening would be to identify patients whose prognosis could be improved with medical therapy or coronary revascularization. When stress testing is performed for the diagnosis of CAD in the general population, many experts recommend standard exercise ECG testing if the resting ECG is normal, since the exercise response will be an important factor in determining prognosis. If the resting ECG has abnormalities that will interfere with interpretation during exercise or if localization of ischemia is expected to be important, an exercise test with imaging can be performed. For patients who cannot exercise, pharmacologic stress testing should be performed.

The sensitivity and specificity of SPECT rMPI in the diabetic patients were 86 and 56 percent for ≥50 percent diameter stenosis and 90 and 50 percent for ≥70 percent diameter stenosis. Test performance was similar with exercise and adenosine and in the non-diabetic patients. When performing dobutamine stress echocardiography, the sensitivity and specificity were 81 and 85 percent, respectively. Currently, neither CMRI or cardiac CT is an alternative to invasive, selective coronary angiography and neither is recommended for screening asymptomatic patients, including those at high risk. Furthermore, the higher rate of extensive coronary calcification in patients with diabetes interferes with the interpretation of

stenosis severity. In the patients with a normal stress rMPI, cardiac mortality was low and equivalent in diabetic and non-diabetic patients for the first two years. However, after two years, there was a sharp increase in cardiac events in the diabetic patients, with the highest risk in diabetic women.

The most cost effective approach to screening and prevention of cardiovascular events in asymptomatic patients with diabetes remains a subject of debate. The 2002 ACC/AHA guidelines for exercise testing made a more limited conclusion that the weight of evidence favors evaluation only in asymptomatic patients with diabetes who plan to begin a vigorous exercise program.

11. The future of stress testing in coronary artery disease

Noninvasive cardiac testing is used for risk stratification for patients with possible acute coronary syndromes. Several testing modalities exist, and each has unique advantages and disadvantages. Patient characteristics, costs, and local resources dictate which of the cardiac tests are chosen. Noninvasive cardiac tests are improving as new diagnostic technologies and methods are being developed. As future studies reveal the true diagnostic characteristics and capabilities of these tests, physicians can better assess patients' risk of coronary artery disease. As with all diagnostic tests, none of the cardiac tests are ideal.

The utility of a recent negative stress test is limited when it is used to determine the risk for acute coronary syndrome (ACS) in a patient presenting to the emergency department with symptoms of angina. Unfortunately, overreliance on negative stress tests is a common reason for misdiagnosis or delays in diagnosis in patients with ACS. It is critical to remember that cardiac tests are useful for risk stratification, but no test is capable of stratifying a patient's risk to zero. Evaluation of patients with acute chest pain in emergency rooms is time-consuming and expensive, and it often results in uncertain diagnoses or patients with chest pain and low risk for short-term cardiac events, outpatient stress testing is feasible, safe, and associated with decreased hospital admission rates. With an evidence-based protocol, physicians efficiently identify patients at low risk for clinically significant coronary artery disease and short-term adverse cardiac outcomes. The role of cardiac stress testing is invaluable. The future of cardiovascular medicine will be not how to treat acute coronary syndromes, but how can we predict them.

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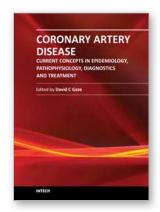
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Coronary Artery Disease - Current Concepts in Epidemiology, Pathophysiology, Diagnostics and Treatment

Edited by Dr. David Gaze

Cardiovascular disease is ranked as the leading cause of death world wide, responsible for 17.1 million deaths globally each year. Such numbers are often difficult to comprehend. Heart disease kills one person every 34 seconds in the USA alone. Although the leading killer, the incidence of cardiovascular disease has declined in recent years due to a better understanding of the pathology, implementation of lipid lowering therapy new drug regimens including low molecular weight heparin and antiplatelet drugs such as glycoprotein IIb/IIIa receptor inhibitors and acute surgical intervention. The disease burden has a great financial impact on global healthcare systems and major economic consequences for world economies. This text aims to deliver the current understanding of coronary artery disease and is split into three main sections: 1. Epidemiology and pathophysiology of coronary artery disease 2. Coronary artery disease diagnostics and 3. Treatment regimens for coronary artery disease

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