Non-invasive Assessment of the Risk of Coronary Heart Disease

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Objective.—Non-invasive evaluations for the presence of coronary heart disease (CHD) are being done with increasing frequency in clinical medicine and as part of the risk selection process for life insurance. The predictive value of testing depends on the pretest probability of disease and the sensitivity and specificity of the testing used. This paper reviews the accuracy of exercise treadmill testing (ETT), myocardial perfusion imaging, stress echocardiography and electron beam computed tomography (EBCT) in the assessment of CHD risk.

Methods.—Literature review using Medline.

Results and Conclusions.—Non-invasive testing is most useful in assessing persons with known or suspected coronary heart disease. Although a low pretest likelihood of disease limits the predictive value in young subjects and subjects with no known risk factors, a positive ETT or EBCT calcium score $>160$ may be viewed as a risk factor for CHD.

EXERCISE TREADMILL TEST (ETT)

Exercise ECG testing is the most widely used non-invasive screening procedure done for assessment of coronary artery disease. Numerous studies have validated that even in asymptomatic populations, an ischemic ST-segment response to exercise is a risk factor, independent of other conventional risk factors, for the future development of coronary events (eg, angina pectoris, myocardial infarction, sudden cardiac death).1-12

However, exercise treadmill testing is primarily indicated for evaluating patients with known or suspected CHD, and for providing prognostic information concerning patients with known CHD. Application of ETT to a population of healthy applicants immediately
Figure 1. Pre-testing Probability of CHD.

incurs the problem of low prevalence in a tested population. Estimates of sensitivity and specificity of testing may be misleading when the prevalence of CHD is low, resulting in a lower predictive value of a positive test than most underwriting physicians would like.

The importance of pre-testing probability of CHD on assessing ETT results was graphically illustrated by Patterson and Horowitz in 1989. The pre-test probability for CHD is low, illustrated in Figure 1 by the left-most bar representing a 45-year-old asymptomatic male with no risk factors, the presence of a positive result on ETT raises the post-test probability of coronary artery disease by only a small amount. Similarly, in a 55-year-old male with typical angina and multiple risk factors (right-most bar), a positive ETT raises the post-test probability also by a relatively small amount. The greatest usefulness of ETT in this illustration is when a 45-year-old male with atypical chest pain is studied. A positive ETT in this setting is seen to increase the likelihood of coronary artery disease from a pre-test risk of 10% to a post-test probability of 65%. In this model, ETT is of greatest usefulness in the assessment of CHD when applied in this latter setting.

Recognizing common causes of a false-positive ETT will obviously increase the accuracy

| Table 1. Indicators of Prognosis on ETT |

Indicators of Poor Prognosis on ETT

- **ECG changes:**
  - Horizontal or downsloping ST segments
  - ST-segment elevation absent “q” wave evidence of a closed coronary artery
  - ST-segment depression >2 mm
  - ST-segment depressions in multiple leads
  - Ischemia early into exercise
  - Ischemic changes persisting >5 minutes into recovery

- **Non-ECG changes:**
  - Chronotropic incompetence (failure to achieve 80% of calculated maximal heart rate) if not on beta blockers
  - Fall in blood pressure with increasing exercise
  - Poor exercise capacity (<5 METs, unable to proceed from Stage I Bruce)
  - Slow heart rate recovery after exercise (failure of HR to fall by 12 beats per minute or more at 1 minute—associated with an adjusted relative risk of death of 2.0 (95% confidence interval 1.5–2.7, p < 0.001))
  - Evolution of chest pain with exercise corresponding with ECG changes

Indicators of Good Prognosis on ETT

- **Good exercise capacity (>8 METs, Bruce Stage 3+)
  - Rapid heart rate recovery after exercise
of ETT in finding occult CHD. Conditions commonly causing a positive ETT in the absence of coronary artery disease include diseases that cause ST-segment depression on the resting ECG, including bundle branch blocks, left-ventricular hypertrophy, digitalis, and pre-excitation syndromes. Mitral valve prolapse is also recognized to cause ST-segment changes on ETT that are unrelated to coronary artery disease. In the setting of these diseases, further ST-segment depression with exercise on ETT does not correlate with coronary heart disease.

False-negative results on ETT (a normal or non-diagnostic ETT in the setting of significant coronary artery disease) may be seen with a history of myocardial infarction, and coronary artery disease limited to a single vessel. It is commonly thought that false-negative ETT also occurs with failure to reach an adequate peak heart rate on exercise, often due to administration of a beta blocking or calcium channel blocking medication. There have been numerous attempts to improve the diagnostic accuracy of ETT by employing multivariate analysis on test variables. These test variables include the amount, onset, duration and configuration of ST-segment depression, duration of exercise, heart rate and blood pressure response to exercise, number of leads showing ST-segment depression, the presence of ventricular arrhythmias, and the presence or absence of exercise-induced chest pain.

Probably the most popular of these “scores” is based on data from Duke University, originally described in 1987 by Mark and colleagues and further validated by Shaw et al in 1998. The Duke Treadmill Score (DTS) is:

\[
DTS = \text{exercise time} - \left( 5 \times \text{ST deviation} \right) - \left( 4 \times \text{exercise angina} \right)
\]

where exercise angina is 0 = none, 1 = non-limiting, and 2 = exercise-limiting.
Table 3. Relative Risks of CAD According to DTS Grouping

<table>
<thead>
<tr>
<th>DTS Score</th>
<th>Significant CAD</th>
<th>Severe CAD</th>
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<tbody>
<tr>
<td>Low-risk</td>
<td></td>
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<tr>
<td>Moderate-risk</td>
<td>3.1-fold increased risk</td>
<td>4.2-fold increased risk</td>
</tr>
<tr>
<td>High-risk</td>
<td>376-fold increased risk</td>
<td>26-fold increased risk</td>
</tr>
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Relative risks in Predicting 5-year Mortality and Cardiac Death

| ST-segment depression >1 mm | 19% |
| Exertional chest pain       | 12% |
| Exercise duration >6 minutes| 13% |
| Low-risk DTS                | 3%  |
| Moderate-risk DTS           | 10% |
| High-risk DTS               | 35% |

Probability of 5-year Survival % by DTS Score

<table>
<thead>
<tr>
<th>Total Points</th>
<th>Probability of 5-yr Survival, %</th>
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<tbody>
<tr>
<td>10</td>
<td>10%</td>
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<tr>
<td>12</td>
<td>25%</td>
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<tr>
<td>50</td>
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<td>93</td>
<td>93%</td>
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DTS scores typically range from −25 to +15, with the following categories usually used:

- Low-risk: score of ≥ +5
- Moderate risk: scores of −10 to +4
- High risk: scores of ≤ −11

They found 36% of their population to be low risk, 55% to be moderate risk, and 9% high risk. High-risk subjects had lower peak heart rates, lower systolic blood pressures, and lower exercise times than low and moderate risk subjects. All high-risk subjects had ≥ 1 mm ST-segment deviation, and 94% had exertional chest pain. Low-risk DTS patients had no coronary lesions 60% of the time, or one-vessel coronary disease 16% of the time. Only 0.4% of high-risk DTS patients were without a significant coronary lesion.

Placement of a subject into 1 of these 3 DTS groups allowed for estimation of risk of significant coronary artery disease (defined as >75% stenosis in a major coronary vessel) and severe coronary artery disease (defined as >75% stenosis in the main coronary vessel and/or >75% stenosis in 3 major coronary vessels). (Table 3)

The role of ETT in screening a healthy population of applicants is uncertain, largely because subjects with a normal or negative study do not undergo angiography, and thus the true prevalence of CHD in the study population is unknown.

There are several studies in the literature that attempt to address this problem. In the early 1980s, a study of airline pilots with negative ETT, who underwent coronary angiography, suggested the sensitivity of ETT to be around 50% and the specificity to be around 80%.
Table 4. Exercise Capacity (METs) on ETT and Mortality

<table>
<thead>
<tr>
<th>% Surviving</th>
<th>METs Achieved</th>
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<tbody>
<tr>
<td></td>
<td>&gt;8</td>
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<tr>
<td>Normal Subjects</td>
<td>5 yr</td>
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<tr>
<td></td>
<td>10 yr</td>
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<tr>
<td></td>
<td>14 yr</td>
</tr>
<tr>
<td>Subjects with CHD</td>
<td>5 yr</td>
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<tr>
<td></td>
<td>10 yr</td>
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<td></td>
<td>14 yr</td>
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Adapted from Myers et al.24

Pilote et al21 examined a consecutive cohort of 4334 asymptomatic adults who participated in exercise treadmill testing as part of a preventive health/executive physical program at the Cleveland Clinic from 1990 to 1993. The median age was 51, and 81% were men. Thirty-four percent had 1 or more cardiac risk factors. Fifteen percent (650 patients) had a positive ETT, and 126 underwent coronary angiography. Severe coronary artery disease (main coronary and/or 3-vessel coronary stenosis > 75%) was identified in 19 subjects, 0.44% of the original cohort (95% CI 0.26% to 0.62%).

Rywik et al22 have shown that in an asymptomatic population, ischemic ST-segment changes that begin after cessation of exercise have an adverse prognostic significance for future coronary events similar to that for ST-segment changes appearing during exercise. Both patterns of ST-segment changes predict an approximate 2.5-fold independent risk for future coronary events compared with individuals with a normal exercise ECG without ST-segment change.

A population-based study done on all persons (1452 men and 741 women) who underwent exercise treadmill testing over a 2-year period in Olmsted County, Minnesota, found that exercise capacity was the variable that exhibited the strongest association with all-cause mortality and cardiac events.23 The strong relationship between maximal exertion attained on ETT and mortality was also the finding of Myers et al24, who found that each 1-MET (metabolic equivalent) increase in exercise capacity conferred a 12% improvement in survival. Myers et al concluded that exercise capacity is a more powerful predictor of mortality among men than other established risk factors for cardiovascular disease. (Table 4)

These findings would seem to agree with spirometric mortality data indicating a strong relationship of abnormal performance on FVC and FEV1 testing to correlate not just with death from respiratory disease, but also with cardiac mortality. An applicant's exertional capabilities, whether it be walking vigorously on a treadmill or blowing through a spirometer for 6 seconds, seems to have significant prognostic significance in underwriting.

One of the largest studies of exercise treadmill testing in asymptomatic men was reported out of the Cooper Clinic in Dallas, Texas. ETT was done on 25,927 healthy men, mean age 42.9 years, from 1970 to 1989 and with an average follow-up of 8.4 years. In men with no history of disease and no risk factors, an abnormal test was associated with a 20-fold increased risk of coronary heart disease death compared with men with a normal test.25 (Figure 2)

As the number of risk factors increased, the
risk of coronary death increased in a linear fashion up to a relative risk of 80 in those with $\geq 3$ risk factors. The risk of death in those with no risk factors, other than an abnormal exercise test, was twice as high as the risk of death in those with $\geq 3$ conventional risk factors, but with a normal exercise test.

The authors concluded that an abnormal exercise test is more powerful by several orders of magnitude than other conventional measures of risk such as elevated cholesterol, cigarette smoking, and high blood pressure.

**MYOCARDIAL PERFUSION IMAGING**

Myocardial perfusion scintigraphy has a sensitivity of 90% in diagnosing coronary artery disease, which is greater than that achieved with ETT.26 Thallium-201 is a potassium analogue, which is taken up by myocardium relative to regional coronary blood flow. Several hours later much of the thallium leaves the myocardial cells, and there is redistribution of tracer throughout the myocardium such that hypoperfused areas with little initial uptake are eventually filled in. Administration of Thallium-201 during exercise exaggerates the regional differences in myocardial blood flow.

Technetium-99m labeled tracers, such as technetium-99m sestamibi (Cardiolite) and technetium-99m tetrofosmin (Myoview), are also used in exercise myocardial perfusion imaging. Sestamibi has a lower myocardial extraction than thallium but a more prolonged residence time in the myocardium and gives superior imaging quality in obese and/or female patients. It also allows for measurement of resting left ventricular function.

Although the sensitivity for detection of coronary artery disease with Thallium-201 is high, it does a much poorer job differentiating patients with more severe disease. Kwok et al27 studied 264 patients who had a single abnormal territory on TI-201 and who subsequently underwent coronary angiography. Twenty-six percent of this group was found to have severe coronary disease, defined as coronary artery narrowing of $> 70\%$ involving the left main coronary artery and/or 3 other major coronary vessels (ie, left anterior descending, right coronary, circumflex, posterior diagonal). They found 4 clinical and exercise variables—diabetes mellitus, hypertension, magnitude of ST-segment depression on ETT, and the exercise rate-pressure product (peak heart rate $\times$ peak systolic blood pressure)—to be independent predictors of severe coronary artery disease. They then studied a separate group of 474 consecutive patients, who were initially treated with medical therapy for a single territory abnormality on TI-201 exercise myocardial perfusion, and divided them into 3 risk groupings (low, medium, and high risk) and followed them for a median of 7 years. The 8-year overall survival rates in the low-, intermediate-, and high-risk groups were 89%, 73% and 75%, respectively.

In an interesting analysis of this data, Verani28 found that patients with no history of hypertension and/or diabetes mellitus and who achieved a rate-pressure product of $> 30,000$ could have up to 2 mm ST-segment depression on ETT and still be in the highest survival tertial. Conversely, patients with both hypertension and diabetes whose rate pressure was $< 24,000$ were in the lowest survival tertial even with ST-segment change of $> 1$ mm. Once again, the importance in pretesting likelihood of disease is emphasized in analyzing ST-segment change on ETT and abnormalities on myocardial perfusion scans.

Pharmacologic stress, instead of exercise, yields results on myocardial perfusion imaging that are identical. Pharmacologic agents used to induce myocardial stress include dipyridamole, adenosine and dobutamine. The agents are used with either perfusion imaging or echocardiography.

Pharmacologic stress testing with dipyridamole or adenosine is more accurate than exercise perfusion studies in subjects with baseline left bundle branch block (LBBB). A major drawback to all pharmacologic testing is that there is no concomitant assessment of functional capacity.

Of particular interest to the life insurance
industry is the specificity of stress perfusion studies. Subjects with a normal stress perfusion study, with or without known CHD, have a risk for future cardiac events < 1% per year, compared to > 7% per year with abnormal scans. Risk increases in relation to the severity of the perfusion deficits.

A common cause for false-positive tests in myocardial perfusion is obesity. One study of 607 patients who underwent exercise Thallium-201 Single Proton Emission Computed Tomography (SPECT) imaging found that obesity (defined as body mass index $\geq 30$ Kg/m$^2$) was associated with lower positive predictive value (86% versus 92%) than found in non-obese patients.

The following defects are probably irrelevant in a patient with good exercise tolerance without ECG changes or symptoms:

- A small, posterior perfusion defect in an obese, stocky male
- A small, anterolateral defect in a female with large breasts
- A small, inferior defect secondary to diaphragmatic attenuation

Advances in perfusion scintigraphy, such as gated SPECT perfusion imaging, allows for measurement of left ventricular ejection fraction during perfusion imaging. In a study of 1680 patients who underwent Tl-201/stress Tc-99m sestamibi gated SPECT and who were followed for an average of 19 months, patients with a post-stress LVEF $> 45\%$ had a mortality rate of < 1% per year, even in the presence of multiple and/or severe perfusion abnormalities. In contrast, those with an LVEF $< 45\%$ had a mortality of 9% per year, even if the perfusion defects seemed mild.

Another advance in perfusion scintigraphy has been simultaneous first-pass radionuclide angiography. Technetium-labeled myocardial perfusion tracers are rapidly injected and allow for estimation of ventricular function and volumes along with differential perfusion. These studies are valuable in providing good images in patients with obesity or obstructive lung disease, and they provide accurate information about the ejection fraction at rest and during exercise. This test is limited by high cost, requires bicycle rather than treadmill exercise, and tends to be inaccurate when the heart beat is irregular (ie, frequent premature beats or atrial fibrillation). Its specificity is also reduced in females and in patients with abnormal left ventricular function at rest.

**STRESS ECHOCARDIOGRAPHY**

Stress echocardiography can be done with exercise, with pharmacologic stressors (eg, dobutamine, dipyridamole, adenosine) or with atrial pacing with transesophageal echocardiography. Atropine may also be given if needed to achieve 85% of maximal predicted heart rate. It detects a contraction abnormality and, therefore, a physiologic change in response to ischemia. Stress echocardiography is felt to be comparable, in terms of sensitivity and specificity, to stress perfusion imaging. It is not felt to provide quite as much information as stress perfusion in the actual identification of the arteries with stenosis, the identification of multivessel coronary disease, or demonstration of myocardial ischemia superimposed upon an area of infarction.

A meta-analysis found that dipyridamole perfusion imaging and exercise echocardiography were equally accurate (77% and 80%, respectively) for detecting myocardial ischemia in patients with an intermediate- to high-pretest probability of disease. Exercise echocardiography is particularly useful for diagnosing coronary disease in the presence of baseline ECG abnormalities that make standard ECG exercise tests uninterpretable. It is probably the test of choice in patients with LBBB on resting ECG, especially if the interpreter of the study knows the patient has LBBB and that abnormal septal motion is commonly seen in this condition. Stress echocardiography is unreliable when significant resting wall motion abnormalities exist, and when patients are either obese or have severe emphysema. Because of the difficulty associated with ex-
exercise 2D echocardiography, dobutamine echocardiography has become increasingly popular. Dobutamine echocardiography is based on the premise that the myocardial region perfused by arteries with significant stenosis will deteriorate when ischemia is provoked by the inotropic and chronotropic effects of dobutamine.

A review of 28 published studies involving 2246 patients reported an overall sensitivity, specificity, and positive predictive value of 80%, 84%, and 81%, respectively. Dobutamine echocardiography may be of particular value in evaluating hypertensive patients with chest pain. Fragasso et al° performed stress/rest sestamibi myocardial perfusion imaging, both dipyridamole and dobutamine echocardiography, and then coronary angiography in 101 patients with hypertension, chest pain, and a positive exercise ECG test. Dobutamine echocardiography was superior to dipyridamole (84% versus 74% sensitivity) and had a higher specificity (80% versus 36%) and positive-predictive value (85% versus 67%) for the diagnosis of coronary disease compared to perfusion imaging.

DETECTION OF CORONARY ARTERY DISEASE IN WOMEN

Treadmill exercise testing has a higher false-positive rate in women than men and a relatively low-predictive value of a negative test. In a meta-analysis of 19 studies of at least 50 women each who underwent both exercise ECG testing and coronary angiography, the sensitivity, specificity, and positive- and negative-predictive values for CHD were 61%, 70%, 85%, and 51%, respectively.°

The negative-predictive value of stress ECG is related to age and the presence of coronary risk factors; it is high in younger women without risk factors, but may be as low as 25% in post-menopausal women with 3 or more risk factors.°°

The factors contributing to the lower sensitivity and specificity of ETT in women is attributed to a lower pretest probability of CHD, particularly multivessel disease, to suboptimal performance, and to a 5- to 20-fold greater incidence of falsely positive ST-segment depression on exercise ECG's, the etiology of which is unknown.°° Thallium-201 perfusion imaging is less than ideal in women because of attenuation due to greater obesity and breast artifact in women compared to men.°°

The use of Te-99m imaging in women improves diagnostic accuracy. In one study, adenosine technetium-99m sestamibi myocardial perfusion SPECT had a sensitivity of 93% and a specificity of 78% for the detection of CHD in women, irrespective of the presenting symptoms or pretest likelihood of disease.°° The overall specificity of dobutamine echocardiography is greater in women compared to men (94% versus 77%) although the sensitivity is the same. The specificity of dobutamine echocardiography in women appears to be greater than that of other techniques.°°

EBCT: ELECTRONIC BEAM (ULTRAFAST) COMPUTED TOMOGRAPHY

EBCT calcium scores done in free-standing radiology clinics as part of a health assessment is the most frequent encounter most underwriting departments have with this technology. A “calcium score” is available within 10 minutes at a cost of $300-$500 in most centers. The test requires minimal patient cooperation and/or preparation, and the radiation dose for a single screening EBCT scan is 82 mRem for men and 150 mRem for women,
EBCT calcium scores and films provide anatomic, rather than physiologic, information. Its validity is based on the premise that calcium burden found in atherosclerosis correlates with active plaque development. Although calcification is more frequently seen in advanced lesions, small amounts of calcification can be detected in earlier stages of atherosclerosis, especially in high-risk subjects. EBCT has successfully detected calcification in patients as young as 11 to 24 years of age with familial hypercholesterolemia, for example.

An increasing number of studies suggest the validity of detection of asymptomatic CHD in low- to moderate-risk subjects using this technology. Table 5 shows the results of a study that followed 1173 asymptomatic subjects for 19 months. Negative-predictive values were 99%, and the odds ratios for development of symptomatic CHD increased to 22:1 and 36:1 for the higher calcium scores. These same patients were reevaluated after an average follow-up of 3.6 years. The mean calcium score for those with a subsequent cardiac event was 764, compared to a mean score of 135 among those without subsequent event. A calcium score > 160 was associated with an odds ratio of 15.8 for a subsequent cardiac event (p < 0.0001).

In another study of 926 asymptomatic subjects followed for 3.3 years, the relative risk for a new cardiac event was compared with EBCT calcium scores. (Table 6) Coronary arteriography was done in 18 asymptomatic and apparently healthy adults with elevated calcium scores (mean calcium score was 573). The mean worst stenosis was 45%, and the worst stenoses were highly correlated with the square root of the calcium score. The authors of this study concluded that most asymptomatic adults with significantly elevated calcium scores on EBCT have significant but non-obstructive coronary artery disease (ie, preclinical obstructive CAD) and that the relation of the calcium score and the severity of the stenosis was highly significant.

While calcium severity on EBCT can identify asymptomatic subjects at risk for CHD, perhaps a more relevant question is whether EBCT calcium scores correlate to the presence of silent ischemia, since silent ischemia is very predictive of future cardiac events. In a study of 411 subjects who had an exercise stress test with myocardial perfusion imaging within a close time period of undergoing EBCT, the likelihood of silent ischemia was found to be increased with increased calcium scores, regardless of sex or age. No subject with a calcium score < 10 had silent ischemia, while 2.6% of those with scores 11-100, 11.3% with scores 101-399, and 46% of those with scores > 400 were found to have evidence of silent ischemia on ETT and/or myocardial perfusion imaging.

Finally, a study involving 207 patients with low to intermediate probability of CHD compared the economic costs of finding and confirming coronary artery stenosis using EBCT, ETT, and myocardial perfusion studies. Patients with EBCT scores of > 160 were considered to have obstructive CAD and then underwent ETT, and subsequently coronary artery angiography if the ETT was positive. This diagnostic approach was 45% to 65% cheaper than if the work-up began with a positive ETT, then progressed to myocardial perfusion imaging and then coronary angiography.

EBCT technological improvements have allowed for measurements of right ventricular (RV) and left ventricular (LV) chamber volumes, LV muscle mass, and regional function following perfusion with Thallium-201 and Technetium-99m tracers. Studies using these improvements are just appearing in the lit-
eration. In an early study comparing rest and exercise EBCT with stress sestamibi SPECT in 33 subjects with chest pain who underwent subsequent coronary angiography, the sensitivity and specificity of EBCT was 88% and 100%, respectively, versus angiography. In comparison, reversible defects on SPECT had sensitivity and specificity of 75% and 71%, respectively.\textsuperscript{54}

**CONCLUSIONS**

There is a variety of non-invasive tests currently used for the assessment of coronary heart disease. These tests are most useful in assessing subjects with either known or suspected coronary disease, yielding both diagnostic and prognostic information. Use of these tests for screening in supposedly healthy populations has been, for the most part, limited to ETT and EBCT. Although a low pre-test likelihood of disease limits the predictive value in the young and subjects with no risk factors, an unexpectedly positive ETT or EBCT calcium score \textgreater{} 160 may be viewed as a risk factor for CHD, and should be judged accordingly.

ETT is a less reliable test in women, and in female applicants perfusion scintigraphy or exercise/dobutamine echocardiography may be preferred if the circumstances or amount of insurance applied for justifies the added cost. In the presence of underlying LBBB, exercise echocardiography may be preferred if the circumstances or amount of insurance applied for justifies the added cost. In the presence of underlying LBBB, exercise echocardiography may be preferred if the circumstances or amount of insurance applied for justifies the added cost.

Evolving improvements in EBCT technology may possibly make this the preferred diagnostic test for departments underwriting large amounts of life insurance, both from economic and predictive information standpoints, in healthy and asymptomatic applicants. However, that day is not here yet, and an unexpectedly high EBCT calcium score must be currently viewed as simply another risk factor, not in and of itself decisive for any underwriting decision, but also not to be ignored.

Finally, MRI and/or PET technology may eventually supplant all of the discussed non-invasive tests, but such technology is at least 5 years or more away from coming into everyday applicability.

**REFERENCES**


