**POSITIVE EXERCISE ECG AND NEGATIVE THALLIUM – A STANDARD RISK?**

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**Introduction**

Coronary artery disease is the leading cause of morbidity and mortality facing the medical director. Clinical information and resting electrocardiograms are often insufficient for the detection of asymptomatic coronary artery disease and in predicting the risk of a cardiac event in applicants with known coronary artery disease.

Many sophisticated tests have thus been developed to allow an early and more accurate diagnosis of coronary artery disease or for use in predicting coronary artery disease prognosis. Unfortunately, few, if any, of these tests are perfect. Results can be negative in applicants with disease and positive in applicants without disease. Therefore, medical directors often cannot be sure that a test result indicates the true state of the applicant.

This article will address a common medical underwriting situation facing medical directors: the applicant with a positive exercise electrocardiogram and negative thallium stress test. Recent advances in thallium scintigraphy will be briefly reviewed. This will be followed by a discussion of the principles and pitfalls of the application of Bayes’ Theorem to sequential testing in the noninvasive diagnosis of coronary artery disease using the exercise electrocardiogram and the thallium stress test. Finally, a practical approach using this common underwriting situation will be given.

**Thallium Stress Testing**

Thallium is a potassium analog that is usually administered intravenously at peak exercise or during infusion of a coronary vasodilator such as dipyridamole or adenosine. It is efficiently extracted by viable myocardium in proportion to its regional blood flow; thus its initial distribution is related to myocardial perfusion and viability.

After the administration of thallium an initial series of images is acquired within 30 minutes and a second series several hours later. Homogeneous distribution of thallium on the initial series of images is considered normal, the presence of one or more defects in thallium distribution in the first set but not in the second set of images is considered to represent ischemia (the phenomenon of defect resolution is called redistribution) and the presence of one or more defects on both sets of images is considered to represent scarred or nonviable myocardium.

Recent studies have shown that myocardial thallium defects that are nonreversible on 4-hour redistribution studies may be associated with improvement in the uptake after successful revascularization or with evidence of viable myocardium as analyzed by positron emission tomographic assessment of glucose metabolism/myocardial blood flow relations. A less well understood pattern of thallium “reverse distribution” or “apparent worsening” is seen commonly after successful thrombolytic therapy for evolving myocardial infarction or successful angioplasty. It is felt to represent non-transmural myocardial fibrosis, most commonly subendocardial infarction in the presence of a non-flow limiting stenosis.

Thallium imaging after intravenous infusion of the coronary vasodilator dipyridamole has been demonstrated to detect coronary artery disease and is diagnostically equivalent to perfusion studies performed after maximal exercise. In contrast to exercise stress testing, dipyridamole thallium scintigraphy is not dependent on the level of exercise achieved, patient motivation or concurrent antianginal medications. The coronary dilating effect of dipyridamole results in a substantial increase in regional blood flow to areas perfused by normal coronary vessels, but abnormal flow reserve is observed in areas supplied by stenotic vessels. This inhomogeneity of flow is detected by abnormal thallium uptake when the radiotracer is injected during peak vasodilative effect of the drug. Redistribution occurs in areas of viable, but hypoperfused myocardial regions comparable to what is observed in exercise scintigraphy.

Initially planar imaging, employing multiple discrete views, much like the anterior and lateral views of the chest x-ray, was used. The utility of planar thallium imaging was enhanced by the development of quantitative techniques for assessing the initial distribution and subsequent washout of thallium. Unfortunately, planar imaging is inherently suboptimal for assessing myocardial perfusion because frequent overlap of normally and abnormally perfused myocardial regions limits its ability to detect, localize and size myocardial perfusion defects. Because of these limitations most laboratories today use single photon emission computed tomography (SPECT) imaging, in which multiple view images are acquired circumferentially and then reconstructed by computer to a single three-dimensional image, identical in principle to x-ray computed tomography.

Direct comparisons have demonstrated superiority of SPECT over planar thallium imaging including enhancement of overall detection of exercise induced ischemia especially in the
circumflex artery distribution, better prediction of extent of disease and more accurate localization of stenosed branches of coronary vessels responsible for a given perfusion defect. An important advance in the clinical utility of SPECT thallium has been the recent development of quantitative analysis for image interpretation which significantly improves on visual analysis of the tomographic slices. Display of the SPECT data in the form of a polar map or "bulls-eye" plot simplifies the interpretation of tomographic slices.

**Probability and Sequential Testing**

In the past few years a rational approach to the interpretation of noninvasive tests for the diagnosis and prognosis of coronary artery disease, has been developed on the basis of simple concepts of clinical epidemiology and biostatistics. Uncertainty may be quantified as the probability that the applicant has coronary artery disease. As a language for expressing uncertainty, probability has the advantage that it is governed by fundamental rules of logic. The effect of new information on diagnostic uncertainty (i.e., the extent to which diagnostic test results alter the probability of disease) can therefore be determined precisely. Interpretation of test results depends in part on other known information about an applicant. A positive test result in an applicant who has a low pretest probability of disease (for example, an asymptomatic 30 year old female insurance applicant) is considerably more likely to be falsely indicative of disease than an identical result in an applicant who has a high pretest probability (for example, an applicant with typical angina). Thus the medical director's expectation prior to looking at the test results is the starting point for using noninvasive tests in underwriting the risk of coronary artery disease.

On the basis of both theoretical considerations and clinical studies, it is now clear that diagnostic information derived from exercise electrocardiograms and thallium perfusion imaging of persons with a low pretest probability of coronary artery disease is limited. However, by applying easily obtained clinical information, one can change pretest likelihood of coronary artery disease and thereby greatly improve diagnostic information derived from a normal or abnormal test result. Probability analysis can further enhance diagnostic accuracy if one applies the principle that when the results of two test procedures are reasonably independent of one another, the post test likelihood of disease derived from the first test can be used as the pretest likelihood of disease for the second.

An important issue for medical directors is what level of post-test probability is required to rule in or rule out coronary artery disease for an individual applicant. A frequently used clinical threshold is in the range of 5–10% (i.e., < 10% probability rules out disease and > 90% confirms disease is present), but this level could and should be varied to suit the clinical and business implications of the application.

To establish the initial pretest likelihood of coronary artery disease, most medical directors use a table similar to that illustrated in Table 1. By assessing the patient's age, gender and specific characteristics of symptoms, it is possible to roughly estimate the probability of coronary artery disease. This estimate can be further refined if one additionally considers such risk factors as: serum lipid status, smoking status, presence or absence of hypertension, diabetes and obesity, as well as the resting electrocardiogram (normal or abnormal).

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<th>Table 1: Pretest Likelihood of Coronary Artery Disease</th>
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*Modified from references (6) and (7)*

The effectiveness of noninvasive tests for coronary artery disease is related to test sensitivity, test specificity and the prevalence of coronary artery disease in the population being tested. If the prevalence of coronary artery disease in the population at hand is known, two other determinations can be made: the positive and negative predictive values of the test (post test likelihood). It is these latter factors that are more directly relevant to the underwriting of coronary artery disease risk. Positive predictive value is defined as the probability that an applicant with a positive test actually has coronary artery disease. Negative predictive value is defined as the probability that an applicant with a negative test does not have coronary artery disease. The precise values for sensitivity and specificity for the exercise electrocardiogram and thallium stress tests vary from center to center and are still evolving with advances in technology. Despite this, an analysis of published data has allowed construction of probability curves relating pretest (prevalence) and post-test (predictive value) likelihood of coronary artery disease for the exercise electrocardiogram and exercise thallium tests (Fig. 1) and (Fig. 2).
Figure 1
Exercise Electrocardiography
ST Segment Response

Family of ST depression curves and likelihood of Coronary Artery Disease. ST ↓ = S – T depression.
A, B and C refer to example #1 and D, E, and F refer to example #2. (Modified from references (6) and (7)).

Figure 2
Thallium Perfusion Scan
Sensitivity 85%, Specificity 90%

Thallium perfusion scanning and probability of Coronary Artery Disease.
A¹, B¹ and C¹ refer to example #1 and D¹, E¹ and F¹ refer to example #2. (Modified from reference (6)).
These likelihood curves are plotted with normal test results on the bottom and abnormal test results on the top. Their interpretation can be further refined by considering additional factors such as the severity of ST segment depression, the number of leads involved, duration of ST segment depression post exercise, peak workload, duration of exercise test, blood pressure response, arrhythmias and double product.

The reported sensitivity and specificity of exercise electrocardiograms are in the range of 60% to 85% respectively. The high number of false positive responses observed in low prevalence population results from a wide variety of conditions that can affect the electrocardiogram. Some of these are technical: signal averaging of the ECG, inadequate skin preparation that results in noise or simply a wandering baseline. Patient related factors can be divided into those due to non-ischemic factors and those that are due to ischemia but a non-atheromatous process. Non-ischemic causes include: drugs, electrolyte abnormalities, hyperventilation, vasoregulatory asthenia, intraventricular conduction defects and WPW syndrome. Left ventricular hypertrophy or hypertension and mitral valve prolapse are common causes of false positive tests most likely on an ischemic basis. In addition there are less common situations in which true ischemia might be present without atheromatous coronary artery disease, such as coronary spasm, left ventricular outflow tract obstruction, abnormal coronary vasodilator reserve and "syndrome X".

The sensitivity of thallium testing for coronary artery disease is in the range of 80-90% and the specificity has been traditionally high, at approximately 90%, although more recent reports have indicated a slightly lower specificity perhaps due to post test referral bias in the population studied.

Some of the false positive thallium defects are most commonly artifactual due to shifting breast artifact, inaccurate patient positioning between stress and redistribution studies, diaphragmatic attenuation of the inferior wall and computer processing errors such as those resulting from over subtraction of portions of the myocardium. Beyond these technical causes, false positive findings occur for similar nontechnical reasons as those for the exercise electrocardiogram. The causes of false positive thallium test, however, are not as numerous or frequent as for the exercise electrocardiogram.

During the last few decades a number of exercise ECG variables have been found to be useful prognostically including: depth of ST segment depression, slope of ST segment depression, duration of ST segment depression in recovery, time of onset of ST segment depression, exercise duration and exercise induced hypotension. Many investigators have found that an abnormal exercise ECG response in asymptomatic individuals is associated with roughly a fivefold increase in risk of cardiac events although the annual frequency in positive responders is relative small. Thallium scintigraphy is a more expensive but also more powerful test of cardiac prognosis than is the exercise ECG because it is a more sensitive and specific marker of ischemia. Thallium scintigraphy gives results which reflect both the extent (proportion of myocardium at risk or number of diseased vessels) and severity (magnitude of ischemia within a given zone or severity of an individual stenosis) of coronary artery disease. The number and location of perfusion abnormalities and presence of increased lung uptake represent important extent variables. Severe perfusion defects and slowly reversing defects represent important severity variables reflecting the presence of high grade (> 90%) stenosis. Three variables have been found to provide independent prognostic information: 1) number of thallium defects, 2) magnitude of the initial reversible defect, and 3) thallium lung uptake.

**Prognostic Implication of Negative Stress Thallium**

Despite the recent advances in thallium scintigraphy, the method is not 100% sensitive and false negative results when compared with coronary angiography still occur. However, it is conceivable that the results of the thallium scintigraphy appropriately reflect the functional significance of disease. The medical director may then reasonably ask: is the technically correct negative thallium stress test able to predict a good prognosis? Some assurance may be gained from the studies looking at the prognostic significance of the negative thallium stress test in patients with chest pain. These studies have consistently shown an excellent prognosis in this group of patients with yearly overall death rates of 0.2 to 0.5% and yearly myocardial infarction rates of 0.6 to 1.2%. This low cardiac event rate is comparable with that reported for patients with chest pain and angio graphically normal coronaries. Further reassurance has been provided recently by the report of Fleg et al on silent ischemia detected by thallium scintigraphy and exercise ECG in asymptomatic low risk volunteers. A concordant positive exercise ECG and thallium stress test identified a small group of predominantly older subjects with a high risk for coronary events over the next 5 years. However, those with discordant results (positive exercise ECG and negative thallium) did not have an increased risk of cardiac events.

**Practical Use of Probability Analysis**

With the above background let us now approach the problem of the applicant with a positive exercise ECG and negative thallium stress test. The following example illustrates the concept. Suppose a 45 year old male who is asymptomatic presents with an exercise ECG associated with 2 mm horizontal ST segment depression at peak exercise (9 minutes of standard Bruce protocol). A subsequent technically correct thallium stress test to a similar workload is negative.

The first step is to determine the pretest likelihood of coronary artery disease by using a table such as illustrated in Table 1. Using Table 1, we see the pretest likelihood of coronary artery disease in a 45 year old asymptomatic male would be approximately 5%. In practice, this figure might be adjusted slightly upward by the presence of other coronary risk factors.

The next step is to determine the post test likelihood of coronary artery disease by using the exercise ECG results and applying them to the probability curves in Fig.1. This may be done by locating the pretest probability of coronary artery disease of 5% (point A) on the horizontal axis of Fig.1 and then locating the coinciding position on the ~2.0mm ST segment depression curve (point B). The post test probability of coronary artery disease may then be read off the vertical axis (point C) and in this example would be approximately 50%. A 50%
likelihood of coronary artery disease falls in the intermediate probability range — not within the rule in or rule out thresholds of most medical directors as alluded to previously. At this point the medical director has several options given the 50% chance of coronary artery disease:

1. offer a rated policy based on your company’s rating schedule
2. postpone pending further evaluation by the attending physician
3. ordering additional testing for cause — in this example an exercise thallium stress test.

Assuming that either of the latter 2 options is elected and the result is a negative thallium, the next step then will be to use this post test probability of coronary artery disease as determined by the exercise ECG (50%) as the pretest likelihood for analyzing the thallium stress test result using the probability curves in Fig. 2. Using the same procedure as with the exercise ECG locate the 50% pre test probability of coronary artery disease on the horizontal axis (point A) and then locate the coinciding position on the lower negative test curve (point B). The post test probability of coronary artery disease may then be read off the vertical axis (point C) and is approximately 10%. This is within our threshold of confidence to exclude functionally significant coronary artery disease and we can with some confidence recommend a standard rating.

A further brief example is necessary to provide perspective and caution about using this approach. Suppose instead we are underwriting a 50 year old male with typical angina. Using Table I, the pretest likelihood of coronary artery disease is approximately 90% (point D) and a subsequent positive exercise ECG with 2 mm horizontal ST segment depression (point E) would increase the post test probability of coronary artery disease (using Fig. 1) to approximately 98% (point F). Although this is well within our threshold of diagnosing definite coronary artery disease; for purposes of illustration, let us suppose that the attending physician statement also includes a report of a negative thallium stress test. How does this affect our underwriting approach? Following the same principle utilized in the first example, we use the exercise ECG post test probability of coronary artery disease (98%) (point D) as the pre test probability of coronary artery disease for the thallium stress test (Fig. 2). We now see that a negative thallium (point E) only lowers the post test probability of coronary artery disease to 90% (point F) which is still within our threshold of definite diagnosis of coronary artery disease. This applicant would then be rated according to your company rating schedule which has been developed to assign ratings for various levels of probability of coronary artery disease.

Conclusion

In this article I have attempted to review the recent advances in thallium stress testing and set forth the implications of probability analysis as applied to underwriting the insurance applicant with a positive electrocardiogram and negative stress thallium test. Several reservations should be noted regarding the specifics of such analysis. The tables and figures are derived from data from an analysis of published reports. These data are often preliminary and incomplete and the results may vary from center to center. The resulting probability estimates are therefore only approximates. In addition many assumptions have been made in calculating the data. For example, the validity of using two tests in the same applicant to increase the reliability of the resulting diagnostic statements derives from the critical assumption that the tests are based on end points that are independent of one another. Although this assumption is probably not entirely valid, clinical experience utilizing the concept of sequential testing has confirmed its usefulness.

The noninvasive tests for coronary artery disease discussed above do not provide a yes or no statement regarding the presence of coronary artery disease, but rather offer a probability statement based on a continuum of risk. A working knowledge of probability analysis will make it easier for the medical director to decide about each applicant’s future risk of coronary artery disease.

REFERENCES