Causes of false-positive thallium-201 images in the diagnosis of coronary artery disease[1]

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In the diagnosis of coronary artery disease, thallium-201 scintigraphy can provide false-positive results. We studied 179 patients with no previous coronary artery bypass surgery who in 1980 had had thallium stress testing and coronary angiography within 3 months of the radionuclide study. Twenty-two patients were identified with 24 segmental defects in thallium distribution in regions supplied by normal coronary arteries. Two patients had primary myocardial disease, 2 had hypertrophic cardiomyopathy, 6 had left ventricular hypertrophy, and 12 had no cardiac abnormality. In a 1983 review of 18 of the 22 patients with false-positive results for coronary artery disease, 8 regions in 6 patients were still considered abnormal. The difference reflected the evolution of interpretation techniques. Identifiable causes of false-positive thallium scans included primary myocardial disease, left ventricular hypertrophy secondary to aortic stenosis, and perhaps hypertrophic obstructive cardiomyopathy. When these diseases are suspected, another method of diagnosing coronary artery disease should be used. Interpretation of the study using corroborative defects in multiple views will improve diagnostic accuracy.

Index terms: Heart, radionuclide studies • Thallium
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Thallium-201 scintigraphy has become an established tool for the diagnosis and characterization of coronary artery disease. It is not a perfect test, and false-positive results can occur. Identifying situations in which such results might be expected could improve the clinical interpretation of a given test in an individual patient and could lead to bypassing this technique in favor of a more defini-

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tive diagnostic tool. Our review was intended to identify the incidence of such false positives and to describe situations in which they might occur.

Methods

Records of all patients who had exercise and recovery thallium-201 scintigraphic studies between 1 July 1980 and 31 December 1980 were reviewed. Those who had undergone coronary arteriography within three months of thallium testing were selected for review. Patients who had undergone previous coronary artery bypass procedures were excluded.

Coronary arteriography was performed by the Sones technique. The estimation of coronary artery narrowing was given by the primary angiographer in the catheterization report at the time of study. For the purposes of this study, angiographic definitions include: (1) significant coronary artery disease: intraluminal narrowing and irregularity compromising the luminal diameter by at least 50% as seen on multiple projections using contrast cinearteriographic techniques; (2) primary myocardial disease: a generalized hypokinesia of all myocardial segments unassociated with significant coronary or valvular disease and often associated with some increase in ventricular volume; (3) left ventricular hypertrophy: prominence of the left ventricular myocardium as assessed by enlargement of papillary muscle shadows and prominence of ventricular trabeculation; (4) hypertrophic obstructive cardiomyopathy: prominence of ventricular myocardium as noted in left ventricular hypertrophy associated with hyperdynamic, cavity-obliterating contractility of the left ventricle and an intraventricular outflow track gradient; and (5) nonobstructive hypertrophic cardiomyopathy: ventricular changes seen in (4) without a measurable gradient.

Exercise was accomplished via the treadmill and the Bruce protocol. At the point of symptom-limited exercise or with the development of 1 mm or more of horizontal or negative-slope ST-segment depression, 2.0 mCi of thallium-201 was injected through a previously placed free-flowing intravenous line. Exercise was continued for another 30 to 60 seconds unless significant clinical instability was present. After a three- to five-minute rest period, the subject was taken for imaging to a room immediately adjacent to the exercise area.

Thallium imaging was done in a standard fashion. Forty-five degree left anterior oblique and 60–70 degree left anterior oblique and anterior views were obtained in that sequence with approximately 400,000 to 600,000 counts per image acquired over a ten-minute period for each. Three to four hours later, the three projections were repeated in the same sequence and time period. The images were obtained via a Technicare series 120 gamma camera with a high sensitivity, parallel-hole collimator interfaced with a Technicare VIP-450 microprocessor. Interpretation was performed with a Technicare VIP-560 microprocessor. A thallium perfusion abnormality was considered to be present if a myocardial region had less than 80% of the scintigraphic activity seen in the most intense region of each view. This assessment was performed after the application of smoothing and count-normalizing techniques which brought the intensity of all images up to that seen in the most intense image while retaining relative pixel-to-pixel count activity ratios.

For this study, the myocardium was divided into six segments: septal, anteroseptal, apical, apical-inferior, inferior, and posterolateral. A false-positive thallium perfusion pattern was considered present if there was abnormal count activity in one of these segments and if the coronary artery division supplying that segment had less than significant obstruction. Scans showing fixed and transient perfusion defects were classed together. Initial thallium interpretations were those done on a day-to-day basis by the attending nuclear medicine physician and entered into the record as part of the formal test report.

Studies identified as showing false-positive results suggestive of coronary artery disease were reanalyzed in July 1983 by one individual (R.T.G.) as part of a larger group of unknown scans. This second interpretation was done without any clinical knowledge of the individual patients and was based upon the assumption that all exercise had been adequate (equal to or greater than 85% of the target heart rate).

A tissue absorption artifact was identified by reduced activity in one region of myocardium unsupported in the same region on different projections, or reduced count rate activity within a region not related to coronary artery distribution. Positioning artifacts were identified by changes in relative configuration of the ventricle as seen in the different projections and by changes in angulation of the septum with reference to the camera head.

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Results

During the six months of this review, 576 patients had exercise thallium-201 studies. Of these, 179 had undergone arteriography within three months and had not previously undergone coronary artery bypass surgery. Twenty-two patients showed 24 segmental defects in thallium distribution in regions supplied by subcritically narrowed or normal coronary arteries. No significant valvular abnormalities were present, although 2 patients had evidence of mitral valve prolapse on contrast ventriculography not associated with mitral insufficiency.

Two patients had generalized left ventricular dysfunction and dilatation suggesting primary myocardial disease, and 2 had hypertrophic, hyperdynamic ventricles considered to represent hypertrophic cardiomyopathy. Six showed myocardial changes suggesting left ventricular hypertrophy; of these, 5 had history of hypertension. The other 12 patients had no cardiac abnormality and accounted for 14 of the 24 false-positive regions (*Table 1*). The distribution of false-positive defects was uniform except for a low number of pure apical errors (*Table 2*).

Eighteen patients' studies were reinterpreted in a blind fashion. The other 4 were not available for restudy because the raw nuclear data had been lost during transfer to long-term storage tapes. These 18 patients accounted for 20 of the false-positive defects. On review, no defect consistent with coronary artery disease was identified in 12. In 6 of these 12, an abnormal filling pattern was noted but attributed to soft-tissue attenuation or positioning artifacts. In one patient with hypertrophic cardiomyopathy, a pattern which in the past had generally been considered suggestive of ischemia was noted, but on review using current interpretation techniques, it was considered to be a normal variant. The other five studies with discordance between the initial and repeat interpretations had no unusual scintigraphic characteristics to explain the initial false-positive interpretation, but were small localized areas in only the septum (2 cases) or posterolateral wall (3 cases). For 6 patients with left ventricular hypertrophy and an initial false-positive reading, 4 images were considered normal on review, and 1 was again abnormal. One was not available for review.

Eight regions (6 patients) were still considered abnormal on reinterpretation. In 5 patients (7 regions), there were no myocardial abnormalities or scintigraphic suggestion of technical difficulty, and stress had been acceptable (greater than 88%) in 4 of 5 patients.

Table 1. Myocardial findings and results of reinterpretation in 24 false-positive myocardial segments

Patient	Segment	PMD	LVH	HCM	Review No. 2
1	Septum				Normal
2	Septum				Same
3	Septum		+		Normal
4	Septum		+		Normal, ST
5	Septum				Same
6	Anteroseptal		+		Normal, ST
7	Anteroseptal				Same
8	Anteroseptal				Normal, ST
9	Anteroseptal				Normal, PC
10	Anteroseptal			+	Normal
2	Apical				Same
7	Apical-inferior				Same
11	Apical-inferior	+			Same
12	Apical-inferior				NA
13	Apical-inferior		+		Same
14	Apical-inferior		+		Normal, PC
15	Inferior				Normal, ST
16	Inferior		+		NA
17	Inferior			+	NA
18	Posterolateral				Normal
19	Posterolateral				Normal
20	Posterolateral	+			NA
21	Posterolateral				Normal
22	Posterolateral				Same

PMD = primary myocardial disease, LVH = left ventricular hypertrophy, HCM = hypertrophic cardiomyopathy, ST = soft tissue absorption, PC = positional changes, NA = not available.

Discussion

Despite the uniformity in stress testing protocol, radionuclide dose, patient positioning, and acquisition of scintigraphic counts during thallium-201 myocardial imaging, there are limitations to this technique. Noncardiac factors and a number of noncoronary heart diseases have been shown to be responsible for results falsely suggesting coronary artery disease.

Tissue attenuation because of obesity, prominent pectoralis musculature, or breast tissue can

Table 2. Distribution of false-positive thallium-201 defects

Septal	5
Anteroseptal	5
Apical	1
Apical-inferior	5
Inferior	3
Posterolateral	5

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produce anterior or lateral perfusion defects. This apparent decrease in regional radioactivity was addressed by Botvinick and Shames[1] and Dunn et al.[2] Both groups showed that breast repositioning could prevent this artifact. In a study by Friedman et al[3] of 32 women with angiographically documented normal coronary arteries, 28 had normal exercise thallium images, and one had a reversible defect suggesting coronary-induced ischemia; 3 had fixed defects in the anterolateral segments suggesting a myocardial scar. As these 3 patients had normal coronary arteriograms and left ventriculograms, the fixed defects were attributed to breast attenuation.

The diaphragm can produce inferior wall perfusion defects, especially when the patient is imaged in the supine position. Johnstone et al[4] showed that the left lateral image obtained in the supine position had a false-positive rate of 5 of 28 patients studied. When these same patients were imaged while positioned on their right side, there was no diaphragmatic attenuation.

The cardiac apex often has fewer scintigraphic counts and can be misinterpreted as being normal in the absence of coronary artery disease. Cook et al[5] showed this in 7 of 13 normal subjects in an early study. Various explanations such as inhomogeneous concentration at the apex or increased relative apical motion have been offered, but the cause is uncertain. Bailey et al[6] did suggest that only apical defects greater than 15% of the left ventricular circumference represent true abnormalities of perfusion.

Dunn et al[2] studied 76 patients with documented normal coronary arteries; 16 (21%) had abnormal scintigrams. On further analysis, scintigraphic patterns inconsistent with coronary artery disease were not based upon supporting defects in more than one standard view. These inconsistencies were attributed to tissue absorption (breast and diaphragm) and to marked apical thinning.

Noncoronary cardiac diseases have been shown to produce positive scintigrams. Pitcher et al[7] studied 23 patients with hypertrophic cardiomyopathy. Sixteen had selective coronary arteriography; all showed essentially normal coronary arteries. In the entire group, 18 patients had abnormal scintigrams. Three abnormal studies were attributable to myocardial hypertrophy alone, but 15 seemed unrelated to the hypertrophic process and showed patterns similar to those seen in patients with significant occlusive coronary artery disease. They suggested that the presence of these scintigraphic abnormalities, in the absence of significant coronary artery disease, might truly reflect ischemia and may explain the anginal syndrome seen in some patients with hypertrophic cardiomyopathy.

Abnormal thallium imaging has also been described in aortic stenosis, idiopathic left ventricular dilatation with myocardial fibrosis, and sarcoidosis. In a study of 11 patients with aortic stenosis and normal coronary arteries, Bailey et al[8] found that 5 had focal thallium perfusion defects and wall thinning, one had wall thinning alone, and another had a focal defect alone. Three of these 11 patients had repeat thallium imaging after aortic valve replacement. Focal defects or wall thinning were no longer demonstrated after exercise. Although these thallium images were falsely positive for coronary artery disease, the authors suggested that a mechanism of exercise-induced angina in aortic stenosis (subendocardial ischemia) was active and that the scans represented true-positive (ischemic) results.

Gewirtz et al[9] studied mongrel dogs by thallium imaging both in their native state and after multiple interventions including partial aortic occlusion, release of that occlusion, ligation of coronary arteries feeding the left ventricular apex, and nitroprusside inducement of hypotension to decrease left ventricular volume. They found that changes in left ventricular volume and regional wall motion influenced myocardial images independent of changes in myocardial tracer distribution; thus, thallium imaging obtained during transient left ventricular dilatation could provide results falsely positive for coronary artery disease, as does nonischemic dilated cardiomyopathy. In human subjects, Losse et al[10] identified 12/12 abnormal myocardial biopsy specimens in a group with anginal pain, normal coronary arteriograms, and abnormal thallium-201 images. That thallium imaging in sarcoidosis may be falsely suggestive of coronary artery disease was shown by Kinney et al.[11] They demonstrated that 14 of 44 patients with sarcoidosis, but without overt heart disease, had defects in the left ventricular myocardium. Their results suggested that most defects were due to myocardial granulomas, but in 2 of 44 patients with documented normal coronary arteries, the thallium defects during stress resolved with equilibrium. The explanation of this phenomenon is uncertain.

Myocardial bridging of the left anterior descending coronary artery has been reported by some to be associated with abnormal perfusion

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patterns as assessed by thallium-201. Greenspan et al[12] and Voss et al[13] studied patients with myocardial bridging of the left anterior descending coronary artery and found no evidence of ischemia by stress thallium-201 scintigraphy. In contrast, Ahmad et al[14] studied 7 patients with isolated left anterior descending coronary artery myocardial bridges in a different fashion. They graded the severity of the systolic narrowing. Of the 4 patients with greater than 75% systolic narrowing, 3 had an exercise-induced perfusion abnormality. They concluded that high-grade systolic narrowing of a normal coronary artery can produce an abnormal perfusion scintigram. Myocardial bridging is seen frequently in patients with hypertrophic cardiomyopathy.[15] It may be that abnormal thallium-201 images in these patients reflect muscle abnormalities rather than impaired perfusion.

In our patients with false-positive thallium images, primary myocardial abnormalities may be associated with patterns similar to those seen in coronary artery disease as 2 patients had primary myocardial disease. Whether hypertrophic cardiomyopathy can be associated with false-positive scans, as others have suggested, cannot be determined. One of our patients was considered to have an unusual but normal variation of filling, and the other patient's scintigrams could not be interpreted. Left ventricular hypertrophy, on the other hand, does not seem to be associated with false-positive results if careful attention is given to the pattern of thinning. This differs from the results reported in the patients with aortic stenosis mentioned above, and may reflect the absence of subendocardial ischemia with effort that has been suggested to explain results in patients with aortic stenosis and left ventricular hypertrophy who have positive thallium scans.

Reinterpretation of these studies included appreciations which were evolving when the initial readings were made in 1980 and which have led to more specific criteria. Greater reviewer caution when interpreting for the second time cannot be excluded entirely, especially in view of the five small borderline defects classed as normal. The improved results, however, do suggest that critical assessment of the study as a whole, rather than dependence upon a single numerical ratio of count activity, is important in achieving a high level of specificity. The seven segments, which were initially falsely positive and stayed so despite adequate stress and "advanced" skill in interpretation, may represent the unavoidable false-positive responses that can be seen in any test. These may, however, reflect true myocardial abnormalities that were subclinical by angiographic criteria. Some type of exercise ventriculographic study or tomographic thallium study (SPECT) might be helpful in assessing these patients in greater detail.

Based on our own other studies, thallium testing probably should not be used to diagnose coronary artery disease in patients with known primary myocardial disease or left ventricular hypertrophy secondary to aortic stenosis. Hypertrophic obstructive cardiomyopathy may be associated with false-positive scans, and again, if the presence of coronary artery disease is in question, coronary arteriography would be the most direct and reliable approach. Finally, patients with unquestionably abnormal scans might benefit from additional dynamic ventricular testing such as radionuclide angiography or digital subtraction angiography.

References

1. Botvinick EH, Shames DM. Myocardial Perfusion Scintigraphy in Nuclear Cardiology: Clinical Applications. Baltimore, Williams and Wilkins, 1979, pp 1–8.
2. Dunn RF, Wolff L, Wagner S, Botvinick EH. The inconsistent pattern of thallium defects: a clue to the false positive perfusion scintigram. Am J Cardiol 1981;**48:**224–232.
3. Friedman TD, Greene AC, Iskandrian AS, Hakki AH, Kane SA, Segal BL. Exercise thallium-201 myocardial scintigraphy in women: correlation with coronary arteriography. Am J Cardiol 1982;**49:**1632–1637.
4. Johnstone EE, Wackers FJT, Berger HJ, et al. Effect of patient positioning on left lateral thallium-201 myocardial images. J Nucl Med 1979;**20:**183–188.
5. Cook DJ, Bailey I, Strauss HW, Rouleau J, Wagner HN Jr, Pitt B. Thallium-201 for myocardial imaging: appearance of the normal heart. J Nucl Med 1976;**17:**583–589.
6. Bailey IK, Griffith LSC, Rouleau J, Strauss HW, Pitt B. Thallium-201 myocardial perfusion imaging at rest and during exercise—comparative sensitivity to electrocardiography in coronary artery disease. Circulation 1977;**55:**79–87.
7. Pitcher D, Wainwright R, Maisey M, Curry P, Sowton E. Assessment of chest pain in hypertrophic cardiomyopathy using exercise thallium-201 myocardial scintigraphy. Br Heart J 1980;**44:**650–656.
8. Bailey IK, Come PC, Kelly DT, et al. Thallium-201 myocardial perfusion imaging in aortic valve stenosis. Am J Cardiol 1977;**40:**889–899.
9. Gewirtz H, Grötte GJ, Strauss HW, et al. The influence of left ventricular volume and wall motion on myocardial images. Circulation 1979;**59:**1172–1177.
10. Losse B, Kuhn H, Kronert H, Rafflenbeul D, Feinendegen LE, Loogen F. Exercise thallium-201 myocardial perfusion imaging in patients with normal coronary angiogram and ventriculogram (abstract). Circulation 1979;**60:**Suppl II:II 148.
11. Kinney EL, Jackson GL, Reeves WC, Zelis R, Beers E. Thallium-scan myocardial defects and echocardiographic abnor-

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malities in patients with sarcoidosis without clinical cardiac dysfunction—an analysis of 44 patients. Am J Med 1980;**68:**497–503.

12. Greenspan M, Iskandrian AS, Catherwood E, Kimbiris D, Bemis CE, Segal BL. Myocardial bridging of the left anterior descending artery: evaluation using exercise thallium-201 myocardial scintigraphy. Cathet Cardiovasc Diagn 1980; **6:**173–180.
13. Voss H, Kupper W, Hanrath P, Mathey D, Montz R, Bucking J. Clinical correlations, lactate extraction, coronary venous bloodflow and thallium-201 myocardial imaging in patients with isolated left anterior descending muscle bridges: normal variant or obstruction? Z Kardiol 1980;**69:**347–352 (summary in English).
14. Ahmad M, Merry SL, Haibach H. Evidence of impaired myocardial perfusion and abnormal left ventricular function during exercise in patients with isolated systolic narrowing of the left anterior descending coronary artery. Am J Cardiol 1981;**48:**832–836.
15. Kitazume H, Kramer JR, Krauthamer D, El Tobgi S, Proudfit WL, Sones FM. Myocardial bridges in obstructive hypertrophic cardiomyopathy. Am Heart J 1983;**106:**131–135.

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