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Do False Positive Thallium-201 Scans Lead to Unnecessary Catheterization? Outcome of Patients With Perfusion Defects on Quantitative Planar Thallium-201 Scintigraphy

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Objectives. We postulated that artifactually abnormal thallium-201 scans are well identified at the time of initial clinical interpretation by experienced readers and do not lead to unnecessary coronary angiography.

Background. Exercise thallium-201 scintigraphy employing quantitative imaging techniques has yielded sensitivity and specificity values of 80% to 90%. There are image artifacts, such as breast shadows, and variants of normal that, if not correctly identified, can lead to a high false positive rate for detection of coronary artery disease.

Methods. Data from 338 consecutive patients with one or more focal thallium-201 defects on quantitative planar images were reviewed. All patients had undergone symptom-limited exercise scintigraphy and were classified as having either artifactual or nonartifactual thallium-201 defects after review of clinical reports.

Results. Of the 265 patients with defects judged to be nonartifactual on clinical readings, 167 underwent coronary angiography, which demonstrated significant coronary artery disease (≥50% stenosis) in 161 (96%) and normal findings in 6. Four of the latter six had documented prior myocardial infarction. The remaining 73 patients (85% female) had thallium-201 defects deemed to be artifactual on clinical readings, chiefly as a result of breast (66%) and diaphragmatic (8%) attenuation or variants of normal (26%). Only 4 (5%) of the 73 patients underwent subsequent coronary angiography; none had coronary artery disease. One had aortic stenosis and two had variant angina. Follow-up (mean 20 ± 2 months) of the 69 patients in this group who did not undergo coronary angiography revealed no deaths and one nonfatal non-Q wave myocardial infarction.

Conclusions. Artifactual defects on quantitative planar thallium-201 scintigraphy are well recognized by experienced interpreters and do not result in a high false positive rate leading to unnecessary cardiac catheterization. The incidence of coronary artery disease is high in patients with thallium-201 defects judged to be nonartifactual, and many patients with perfusion defects and angiographically normal coronary arteries have organic heart disease.

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Exercise thallium-201 scintigraphy employing quantitative planar imaging techniques has yielded sensitivity and specificity values of 80% to 90% (1–7). When only qualitative visual analysis of thallium-201 images is performed, a lower specificity may result (8,9). The cost-effectiveness of exercise thallium-201 imaging has been compared unfavorably with that of positron emission tomography imaging because of the presumption that a higher false positive rate for thallium-201 imaging leads to unnecessary coronary angiography (10).

We postulated that artifactually abnormal thallium-201 scans are well identified at the time of initial clinical interpretation by experienced readers and do not lead to unnecessary coronary angiography. To test this assumption, we retrospectively reviewed the clinical and exercise thallium-201 scintigraphic reports from 338 consecutive patients who demonstrated one or more focal defects on quantitative planar thallium-201 images (1,3). In addition, we obtained information relative to patient outcome after the exercise imaging study.

Methods

Study patients. The study group consisted of 338 consecutive patients (206 men, 132 women, with a mean age ± 1 SD of 59 ± 10 years [SD]) who underwent exercise testing at the University of Virginia Health Sciences Center during a designated 6-month period and had one or more focal thallium-201 defects on quantitative planar images. The only criterion for inclusion in the study was a thallium scan that was originally interpreted as showing at least one segment

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with a significant reduction in thallium-201 uptake by quantitative analysis (1,3). These scan reports were then classified as abnormal on the basis of either artifactual or nonartifactual findings, a judgment based solely on the text of the official report sent to the referral physician. Four readers were involved in the generation of these clinical scan reports, all of them experienced in thallium-201 scan interpretation. Patients with thallium-201 scans interpreted as artifactual or variants of normal were followed up by telephone contact or review of medical records, or both.

Exercise testing. All patients underwent a symptom-limited exercise test. Medications were not withdrawn before the test. Baseline electrocardiogram (ECG), heart rate and blood pressure were recorded at rest, at each minute of exercise and at 1, 2, 3 and 5 min after exercise. Exercise was terminated when fatigue, claudication, angina, dyspnea, hypotension or ventricular tachycardia (≥10 beats) occurred. Results of an exercise ECG were considered abnormal if the tracing exhibited a normal baseline ST segment at rest with horizontal or downsloping depression ≥1 mm or upsloping depression ≥2 mm 0.08 s after the J point during exercise (11). They were also considered abnormal if baseline ST segment depression increased by ≥2 mm during exercise in the absence of left bundle branch block, left ventricular hypertrophy or digitalis therapy. The exercise ECG was considered nondiagnostic if 1) the patient did not achieve ≥85% maximal predicted heart rate (11) and the exercise ECG showed no ischemic ST depression, 2) the ECG at rest showed left ventricular hypertrophy or left bundle branch block (12), or 3) the patient's medical regimen included a digitalis preparation at the time of the study (13). The exercise blood pressure response was considered abnormal if pressure either decreased or did not increase by ≥10 mm Hg over that recorded at rest.

Thallium-201 imaging. At peak exercise, 2.0 to 3.0 mCi of thallium-201 was injected intravenously and the patient was encouraged to exercise for an additional 30 to 60 s. Initial (5 min after exercise) and delayed (2.5 to 3 h later) images were acquired in the anterior and 45° and 70° left anterior oblique projections by methods previously described (3). Quantitative analysis of the serial images was performed with a computer-assisted count profile method (3). Thallium-201 activity in a segment was generally considered abnormal if it was ≥25%, less than that of the segment with the greatest count intensity in that view (except in the inferior segment, where thallium-201 activity was considered abnormal if it was reduced by ≥35% [3]). Redistribution was considered present if the ratio of the activity in the segment with reduced thallium-201 uptake versus the segment with maximal activity was significantly greater in the delayed than in the initial images (3). A second dose of thallium-201 was not given because data from our laboratory (14) demonstrate no significant enhancement of defect reversibility with reinjection compared with redistribution using quantitative scan analysis on exercise and rest planar images. As long as no image artifact or variant of normal was identified, scans were interpreted as abnormal if a significant defect was present in the initial image by our quantitative criteria.

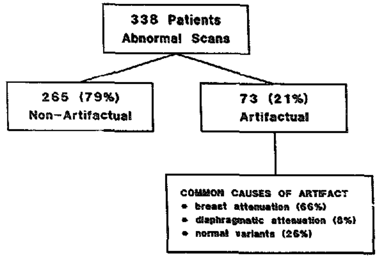

Figure 1. Number of patients in this study judged to have artifactual or nonartifactual thallium-201 defects as the cause of scan abnormalities. Common causes of image artifacts are listed.

Coronary angiography. All coronary angiograms were assessed by visual analysis by an experienced angiographer. Coronary artery disease was defined as ≥50% lumen diameter narrowing of one or more major coronary arteries or their branches (15).

Data analysis. Patients were classified as having either artifactual or nonartifactual thallium-201 defects, as determined from review of the text of the clinical reports, and as having or not having undergone coronary angiography. Group differences were analyzed statistically by the Student t test for differences in age, maximal heart rate with exercise and metabolic equivalents (METs) attained and by the Fisher exact test for differences in gender, exercise test results, prevalence of coronary artery disease and referral to coronary angiography.

Results

Characteristics of patient groups. There were 338 patients with abnormal exercise scintigrams. A total of 265 patients (79%) had, by quantitative criteria, significant thallium-201 defects that were judged to be nonartifactual at the time of initial clinical reading and were therefore interpreted as true positive scans (Fig. 1). Seventy-three patients (21%) had thallium-201 defects judged to be artifactual at the time of initial clinical reading, most often attributed to breast or diaphragmatic attenuation or normal variants (Fig. 1). Table 1 compares data from the 265 patients with nonartifactual thallium-201 defects on quantitative planar imaging with the 73 patients judged to have artifactual thallium-201 defects. When compared with patients with defects read as nonartifactual, those with artifactual defects were younger (55 ± 9 vs. 60 ± 10 years, $p < 0.0005$), more likely to be women (85% vs. 26%, $p < 0.0001$), less likely to have an abnormal exercise ECG (4% vs. 25%, $p < 0.0001$), and more able to

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Table 1. Comparison of Patients With Nonartifactual and Artifactual Thallium-201 Defects on Quantitative Planar Imaging

	Thallium-201 Defects		
	Nonartifactual	Artifactual	p Value
Patients (no.)	265	73	
Age (yr)	60 ± 10	55 ± 9	< 0.0005
Women (%)	26	85	< 0.0001
Exercise ECG (%)			
Normal study	14	45	< 0.0001
Abnormal study	22	4	< 0.0001
Nondiagnostic study	61	51	NS
Peak exercise heart rate (beats/min)	126 ± 24	145 ± 22	< 0.0005
METs (no.)	7.0 ± 2.8	8.1 ± 2.8	< 0.0005

Unless otherwise stated, data are presented as mean value ± SD. ECG = electrocardiogram; METs = metabolic equivalents.

Table 2. Comparison of Patients Undergoing and Not Undergoing Coronary Angiography

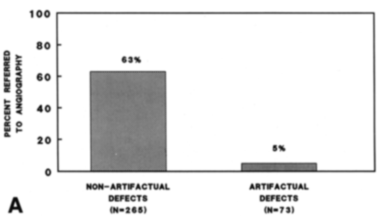
	Angiography	No Angiography	p Value
Patients (no.)	171	167	
Age (yr)	60 ± 10	58 ± 9	NS
Women (%)	27	51	< 0.0001
Exercise ECG (%)			
Normal study	12	30	< 0.0001
Abnormal study	30	9	< 0.0001
Nondiagnostic study	58	61	NS
Peak exercise heart rate (beats/min)	121 ± 25	139 ± 21	< 0.0005
METs (no.)	6.6 ± 2.9	7.8 ± 2.7	< 0.0005

Unless otherwise stated, data are presented as mean value ± SD. Abbreviations as in Table 1.

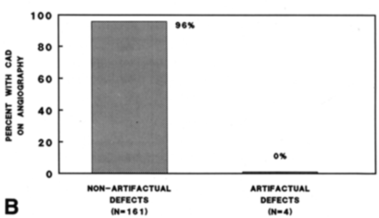
attain a higher heart rate (145 vs. 126 beats/min, $p < 0.0005$) and work load (8.1 ± 2.8 vs. 7.0 ± 2.8 METs, $p < 0.0005$) during exercise testing.

Of the total of 265 patients with significant thallium-201 defects judged to be nonartifactual and indicative of coronary artery disease at the time of scan interpretation, 167 (63%) were referred for coronary angiography by their primary physician (Fig. 2A). Of these 167 patients referred for angiography, 96% had angiographic evidence of significant coronary artery disease (Fig. 2B). As shown in Figure 2, patients with presumed artifactual defects were less likely to undergo coronary angiography and less likely to have coronary artery disease documented by coronary angiography. Of the 73 patients with abnormal scans judged to be secondary to image artifacts at the time of initial clinical interpretation, only 4 (5%) were referred for coronary angiography (Fig. 2A). None of these four patients showed angiographic evidence of significant coronary artery disease (Fig. 2B).

Figure 2. A, Percent of patients with nonartifactual and artifactual defects referred for coronary angiography. B, Percent of patients with nonartifactual and artifactual defects referred to coronary angiography who demonstrated significant angiographic coronary artery disease (≥50% stenosis).



A



B

Coronary angiographic data. Table 2 compares for all 338 patients in the study the data from the 171 patients who underwent coronary angiography with the data from the 167 patients who did not undergo angiography. Those who did not undergo angiography were more likely to be women, less likely to have an abnormal exercise ECG and more likely to attain a higher heart rate and work load during exercise testing. The mean age of patients undergoing and not undergoing angiography was not significantly different. The exercise ECG was nondiagnostic in 61% of patients not undergoing angiography and in 58% of patients referred for angiography (p = NS).

Patients with artifactual thallium-201 defects. Eighty-five percent of the 73 patients with an artifactual defect were women. No difference in age between men and women was observed in this group. The prevalence of women was significantly higher than that in the group with nonartifactual scans ($p < 0.0001$). In the total group of 338 patients, 46% of women had artifactual thallium-201 defects, compared with 5% of all male patients in the cohort ($p < 0.0001$). Of the 73 patients with artifacts, breast attenuation was seen in 66% of patients, diaphragmatic attenuation in 8% and variants of normal in 26% (Fig. 1). Only 3 of these 73 patients had a diagnostic ECG stress test with ischemic ST depression. Four patients (5%) in this group underwent coronary angiography and none had evidence for coronary artery disease (Fig. 2B). Of these four patients, two had documented variant angina by clinical criteria, one had symptomatic aortic stenosis and one had atypical chest pain not thought to be due to cardiac disease. Two of these patients had a normal and two had a nondiagnostic exercise ECG. None of the four had documented cardiac events at the time of follow-up.

Sixty-nine of the 73 patients in this group were not referred for coronary angiography although they had quantitatively significant defects. During a mean follow-up interval of 20 ± 2 months, one patient had experienced a documented nonfatal, non-Q wave myocardial infarction. This patient was a 68-year old woman who had a non-Q wave myocardial infarction 3 months after the exercise thallium-201 scan was performed. The original scan revealed a defect in the anterior wall judged to be a breast attenuation artifact. The patient exercised to a level of 7 METs and attained a heart rate of 114 beats/min, representing 75% of her age-predicted maximal heart rate. Cardiac catheterization performed after the infarction revealed a 70% stenosis of the left circumflex coronary artery and normal left anterior descending and right coronary arteries. After angioplasty was performed on the left circumflex lesion, she experienced no further cardiac events. Results of an exercise thallium-201 study performed 4 months after angioplasty were normal except for the presence of the anterior wall breast artifact. Thus, nearly all of the patients with an abnormal scan due to artifact presumably representing false positive results did not undergo angiography and had an excellent short-term prognosis.

Patients with abnormal thallium-201 scintigrams and angiographically normal coronary arteries. Of the 167 patients with abnormal thallium-201 scans deemed to be nonartifactual and consistent with coronary artery disease who subsequently underwent coronary angiography, 6 (3.6%) were found to have normal coronary arteries. Of these, four had a previous myocardial infarction documented by abnormal creatine kinase, MB fraction elevations and typical symptoms or ECG abnormalities consistent with ischemic injury. As stated earlier, three of the four patients with artifactual thallium-201 defects who had normal coronary arteries on subsequent angiography had some organic heart disease. Two had Prinzmetal's variant angina and one had aortic stenosis. These three patients may have been referred to catheterization on the basis of heart disease that was already recognized before thallium-201 imaging.

Discussion

Advantages and limitations of the study. *Patient outcome.* The data from this study show that although there is a significant incidence of artifacts in thallium-201 studies (16,17), the artifacts can be recognized and need not lead to unnecessary coronary angiography. Only 4 of 73 patients with abnormalities on quantitative planar thallium-201 images thought to be artifactual were referred for coronary angiography. None of these four had coronary artery stenoses, but three of the four underwent cardiac catheterization for clinical indications unrelated to the thallium-201 findings. Two had Prinzmetal's variant angina, and one had symptomatic aortic valvular stenosis. Among 265 patients with abnormal thallium-201 studies judged not to be artifactual, 167 were referred for cardiac catheterization and coronary artery disease was found in 161 (96%). Of the six without significant coronary disease, four had documented prior myocardial infarction. Thus, only two (1.2%) patients among the 161 referred for cardiac catheterization with a positive scan judged to be nonartifactual were found to be free of significant coronary artery or myocardial disease.

Because most of the 73 patients with abnormal scans judged to be due to artifact did not undergo catheterization, we cannot know how many of these had significant coronary artery disease. However, these patients had an excellent short-term outcome during follow-up; none died and only one had an event (a nonfatal non-Q wave infarction). This event rate of slightly <1%/year is similar to that reported by our group (18) in 345 patients with chest pain and a normal quantitative myocardial perfusion scan. The one patient with an event was a woman originally judged to have an anterior "breast artifact" who had a non-Q wave infarction secondary to a single 70% left circumflex artery stenosis. Angioplasty was performed, and results of a subsequent thallium-201 scan were entirely normal except for the same breast artifact. Thus, this patient's original scan appeared to have been a genuinely false negative study that failed to detect an isolated left circumflex artery stenosis.

Effect of available clinical data. Clinical readings of thallium-201 imaging data are subject to bias, but we believed it would be inappropriate to substitute totally blinded research readings in this study because we were interested in the relation between clinical interpretation, patient management and outcome. Because age, gender, height, weight and other clinical data are available in all patients at the time of scan interpretation, it is likely that if such information were known by an interpreter, a borderline persistent anterior defect in a young woman would be read as a "breast shadow artifact." A similar defect might be interpreted as nonartifactual in a patient that recently ruled in for an anterior myocardial infarction. Thallium-201 scan reports in our institution are dictated independent of rest or exercise ECG interpretation. Information relevant to the ECG response to exercise is not factored into the interpretation of the thallium-201 imaging study. The extent to which clinical information adds independently to interpretation of thallium-201 imaging studies is difficult to determine. Internal quality assurance studies in our laboratory have failed to prove statistically significant differences in interpretation with and without clinical data. It appears that clinical data can add considerably to the confidence level of the interpreter but have only a marginal effect on interpretation. It would require a more extensive and cleverly designed experiment

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to definitively test for the amount of influence and statistical independence of clinical information on the final interpretation.

Recognition of artifacts. The judgment of artifact thus appears to be predominantly based on pattern recognition in the raw images. Reviews describing image artifacts for planar and single-photon emission computed tomography (SPECT) imaging have been published (16,17). We view standardized raw images with no background subtraction or contrast enhancement. Artifacts caused by breast or skinfold shadows or attenuation below the line of the left hemidiaphragm can usually be recognized because the shadow line passes across and extends outside the heart or the shadow changes position on the heart with different projection angles, or both. Breast artifacts are the most common and most troublesome. They compromised 66% of the artifacts recognized in the present study. The addition of the breast markers used by Wackers (16) can be helpful if used skillfully, but we find that a good raw image will show the shadows adequately. Normal variant apical thinning, variant positions of the aortic and mitral valve anuli and diminished inferior wall activity due to the overlying right ventricular blood pool are other variants recognized as artifact.

Most of the same artifacts we found to be important appear in SPECT as well as planar studies (16,17). The artifacts can be more difficult to recognize after computer reconstruction of cross-sectional images because the extension of the artifact outside the heart is lost. There is the additional possibility of reconstruction error resulting from patient motion (19), "upward creep" of the heart (20) and bull's-eye reconstruction error (17). However, the best quality control for SPECT studies is to review the sequence of planar projection images that constitute the input data for SPECT reconstruction. Artifacts are recognized on these images exactly as on the planar images discussed.

Comparison with SPECT. False positive rates of 50% for thallium-201 scans have been cited (10) in analyses of the relative cost-effectiveness of positron emission tomography. It was assumed that a high false positive rate from thallium-201 scans would cause more cardiac catheterization, resulting in higher overall expense of medical care. The results of our study show that this assumption is incorrect, at least with quantitative planar thallium-201 scintigraphy. In our study of 265 consecutive cases, only three patients referred for catheterization were found to have normal coronary arteries and no evidence of heart disease. Only two of these had had false positive thallium-201 studies. Unlike visual planar or visual SPECT thallium-201 imaging, quantitative planar or quantitative SPECT imaging (21) is associated with a higher specificity for coronary artery disease detection.

Clinical implications. This study shows that artifacts on thallium-201 studies that could lead to false positive results and increased incidence of unnecessary cardiac catheterization can be recognized. The interpretation of an image artifact does not increase referral for cardiac catheterization. The follow-up studies of patients judged to have artifact indicated a good short-term prognosis. The incidence of death or myocardial infarction among these patients is comparable (about 1% per year) to that among patients being evaluated for chest pain who had completely normal imaging studies.

Standards for test interpretation are subject to a wide variation. Interpreters can achieve very high sensitivity at the expense of specificity and avoid possible false negative results by reading any abnormality as positive. Our results suggest that efficacy and cost-effectiveness are enhanced by balancing sensitivity and specificity and differentiating defects that are more consistent with artifact than with coronary artery disease. This reduces false positive results and does not significantly increase the number of hard cardiac events associated with false negative test results. Similar studies using SPECT and technetium-99m imaging agents are warranted to help establish the most efficacious standards for test interpretation.

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