The Use of Computer-Assisted Diagnosis in Cardiac-Perfusion Nuclear Medicine Studies: A Review

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The use of computer-assisted diagnosis has become widespread in cardiac nuclear medicine. Quantitative programs are commercially available for ventriculography, phase analysis, and thallium 201 perfusion studies. The goal of these programs is to eliminate interobserver variability by objectively analyzing the studies without causing a loss of accuracy. In addition, by using quantitative data not apparent on visual inspection, some programs attempt to increase sensitivity for disease above that possible by the visual reading of images. Programs that analyze perfusion studies to detect coronary artery disease have received the most interest. Results have varied, but sensitivities as high as 95% have been reported. This review discusses the techniques of computer-assisted diagnosis for thallium 201 myocardial-perfusion studies. The circumferential and washout profile methods are discussed in detail.

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UNLIKE MOST subspecialties of radiology, nuclear medicine uses computer-assisted diagnosis on a daily basis. This is especially true in cardiac imaging. Left ventricular ejection fractions are automatically determined from radionuclide ventriculograms with little or no observer interaction.¹ Algorithms define left ventricular volume, determine the end-systolic and end-diastolic frames, assign a background region, and calculate the ejection fraction.²

Phase analysis of radionuclide ventriculograms is performed to determine the timing of atrial and ventricular contraction in the cardiac cycle.³ This is used to diagnose conduction and contraction abnormalities such as reentry arrhythmias and aneurysms.

Recently, the greatest interest in computer-assisted diagnosis (CAID) has been for cardiac-perfusion studies with thallium 201 and the

newer technetium 99m agents sestaMIBI (Du Pont, Billerica, MA) and Teboroxime (Squibb Diagnostics, New Brunswick, NJ).⁴⁻⁶ These programs have several goals (Table 1).

First, the programs are objective and thereby reduce interobserver variability. Some disagreement between observers in interpreting ²⁰¹Tl scans occurs in one third of cases, with significant disagreements in 20%.⁷ In fact, in 13% of exercise-rest ²⁰¹Tl studies, one observer interprets the results as normal while a second diagnoses coronary disease. Agreement for the anatomic location of an abnormality is even worse, ranging from only 11% to a high of 79%.⁸

A second goal of CAID is to interpret cardiac-perfusion studies with an accuracy equal to that of a human expert. This allows less experienced observers to perform and interpret cardiac perfusion studies on-site. CAID also provides a teaching platform that allows physicians to improve their visual interpretation skills through experience with the program.

A third, more ambitious goal of CAID is to increase the sensitivity of perfusion studies for coronary artery disease beyond that possible by human experts. This is attempted using two approaches. First, CAID can better quantitate radiopharmaceutical concentration and more accurately compare activity at stress and redistribution than is possible by visual review. Cases of

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Table 1. Goals of CAID

Reduce interobserver variability
Provide interpretation equal to a human observer—useful for the less experienced
Increase sensitivity over visual reading

subtle degrees of ischemia can be detected in this way. Second, CAID can use criteria that cannot be applied visually such as the washout of ^{201}Tl with time. It has been shown that washout analysis can detect ischemia not seen visually.⁹ Cardiac CAID programs are usually structured to evaluate the parameters listed in Table 2.¹⁰

Perfusion defects are identified by comparing the activity in each region of a patient's left ventricle with a file of the distribution of activity in normals. A second technique, more commonly used in CAID outside the heart, is to compare the activity in one segment of the organ with that in another organ segment in the same individual who is assumed to be healthy.¹¹

CIRCUMFERENTIAL PROFILES

One of the first approaches to quantitation of planar ^{201}Tl scans was to create four transverse slices of activity 1 pixel wide evenly spaced through the left ventricle.¹² Count profiles were created that had a rapid rise and fall as the profile entered and exited the ventricle's muscle mass, with a central valley in slices that passed through the ventricular cavity. Unfortunately, the apex and base of the heart were not evaluated; nor were portions of the myocardium between slices.⁹ For this reason, the circumferential profile was created.

Technique

The circumferential profile takes the elliptical or circular activity present on the digital images, splits it at the top, and straightens it out so it is displayed linearly. The relative counts are plotted on a graph as a function of their angular location from 0 to 360° (Fig 1). This allows both absolute activity per segment and

Table 2. Parameters Evaluated by Cardiac CAID

Identify perfusion defects
Determine whether defects are artifact or real
Differentiate ischemia from infarct
Assign abnormality to a vascular distribution

Fig 1. Normal circumferential ^{201}Tl distribution profile. The abbreviations along the bottom of the graph indicate the segment involved moving from 0° to 360°. The vertical axis is the percentage of maximum counts in the image. The black squares are the counts in each 10° arc of the ventricle at exercise; the white boxes are the normalized redistribution counts. The black and white solid lines represent the lower limits of normal for stress and redistribution, respectively.

relative distribution to be displayed simultaneously.^{13,14} Quantitation is performed spatially by comparing the relative activity of adjacent segments and temporally by measuring the change in activity in a segment with time.¹⁵ This process is divided into five parts (Table 3).

To use quantitative techniques, strict adherence to an acquisition protocol is necessary or a significant number of false-positives will occur. This includes using identical doses of ^{201}Tl , imaging patients at the exact same times postinjection, and using the correct order of acquisition and camera angle for each view. The exact acquisition parameters vary between CAID programs.

If a region of interest is placed over the heart, a significant portion of the measured activity is in overlying and underlying structures as well as in adjacent organs (via scatter). This is sometimes referred to as "tissue cross-talk." For this reason, background subtraction must first be performed.¹² The distribution of tissue cross-talk is nonuniform; therefore, it cannot be treated as a constant. In addition, it changes with time.

The most commonly used technique, developed by Goris and modified by Watson, is a

Table 3. Space/Time Quantitation of Planar ^{201}Tl Scans

Acquire images using special imaging protocol
Process images (background subtraction and smoothing)
Create spatial circumferential profile of relative activity
Create temporal washout profile
Compare the spatial and temporal profiles with normal file

bilinear interpolative background subtraction.¹² A rectangular boundary region is drawn that encloses the heart. The background over the heart is computed by drawing perpendicular lines through each interior pixel and taking the counts where these lines intersect the box's edge. A weighted average based on the interior point's distance from each edge of the box is used. The weight factors are inversely related to the distances between the interior point and the box's edge to prevent discontinuities that can occur at the boundary region. A constant is used to cause a rapid falloff of counts in regions where the box's boundary crosses organs with high counts, such as the liver.

After background subtraction, the images are smoothed using a standard 9-point weighted smoothing algorithm.^{15,16} The circumferential profile is obtained next.

In the technique of Garcia et al, the operator manually identifies the center of the left ventricle.^{15,16} The program then plots 60 radii at 6° intervals in a clockwise direction. Next, the program finds the pixel with the highest counts along each radius. The maximum range for the program to search is assigned by the operator to prevent the program from searching outside the left ventricular wall into other contiguous structures such as the right ventricle. The computer operator then marks the apex on the circumferential profile by visual inspection of the images and the shape of the stress profile. The computer shifts that point to coincide with 90°. Profiles are automatically plotted for each view for both stress and redistribution. Stress images have more total counts than redistribution images because of the washout of ²⁰¹Tl with time, so it is difficult to directly compare the two curves on the same display. To facilitate comparison, the curves are normalized to the maximum pixel value found in any of the profiles. Temporal washout profiles are created next (see Washout Profiles below). Finally, the spatial and temporal profiles are compared with a file of normals.

Normal files are generated from individuals with a low likelihood of coronary artery disease,^{15,16} patients with a less than 1% to 3% probability of having coronary artery disease based on history and nonimaging test results (see both sections on Normal Files below). The

shape of the lower-limit-of-normal distribution is characteristic for each view. The criteria that Garcia et al found gave the best trade-off between sensitivity and specificity for coronary artery disease are shown in Table 4.^{15,16}

Wackers et al have also developed a circumferential program for planar ²⁰¹Tl scans that is similar to the program described above.⁹ However, these investigators subdivide the left ventricle into 36 segments of 10° each. They also differ from Garcia et al by using 2 SD below the mean as the lower limit of normal and requiring a defect to be 50° (five contiguous radii) in size on stress or washout profiles. Only one 50° arc must be abnormal to diagnose coronary artery disease with their technique.

In addition to diagnosing coronary disease, these programs can localize the abnormality to a specific coronary vessel. In general, defects involving the anterior wall (anterior and left lateral views) or the interventricular septum (45° left anterior oblique [LAO] view) are assigned to the left anterior descending artery, inferior defects (anterior and left lateral views) to the right coronary artery, and posterolateral wall defects (45° LAO view) to the circumflex artery.¹⁶ Examples of an infarct and ischemia on circumferential profile are shown in Figs 2 and 3.

Maximum Versus Mean Counts for Profiles

Garcia et al base their technique on the maximum counts in a segment.¹⁵ This value is compared with the normal file. There are a number of theoretical problems with this approach.⁹ First, the assessment of a segment is based on the counts in only 1 pixel. The activity in 1 pixel may not always accurately reflect what is happening in the rest of a segment because the average segment consists of approximately

Table 4. Criteria for an Abnormal Circumferential Profile Study

Any 18° segment (three contiguous 6° radii) in which counts fall more than 2.5 SD below the mean on stress images
Slow washout, defined as any 18° segment with a washout profile more than 2.5 SD below the mean
For the diagnosis of coronary artery disease, at least two of the above abnormalities (two or more abnormal 18° arcs) are required on combined circumferential and washout profiles in the three planar views

Fig 2. Circumferential profile showing an infarct. The exercise and redistribution points are below the normal line in both the BS and AS segments. This indicates an infarct in this region.

22 pixels.⁹ For example, hot spots caused by papillary muscles or unknown causes are occasionally present that may falsely elevate the maximal counts in a segment.¹⁷ Second, the pixel with the maximum counts at stress may not be the same pixel that is chosen for comparison at redistribution. This makes determination of reversible ischemia versus infarct more difficult. In addition, washout data based on the count differences between two different pixels would not be accurate. Third, because the computer algorithm searches for the pixel with maximum activity, it can bypass pixels that may represent a defect if there are some uninvolved pixels in the segment. Finally, quality control may be difficult

Fig 3. Circumferential profile showing ischemia. The exercise points are below both the normal limit line and the redistribution points in the BS and AS segments.

because data based on maximal count density may conceal poor statistics in marginal studies.

To test the hypothesis that using mean counts is superior to maximal counts, Wackers et al processed 98 patient studies using both techniques.⁹ Circumferential and washout profiles were generated. They found that the maximal activity in a segment was 20% to 25% greater than the mean activity. However, the computer graphics generated by both techniques were comparable in 95 of the 98 patients. Using maximum counts per segment, 72 of 80 patients with coronary artery disease were detected, whereas mean count processing detected 71 patients. Thus, the sensitivities (90% for maximum and 89% for mean counts) were not significantly different. Of 18 patients with normal coronary arteries by angiography, 15 were classified as normal using maximum counts compared with 17 using mean counts. This translates into a slightly better specificity using mean segment counts (94%) compared with maximum counts (83%).

Normal files

Although it might seem logical to base normal files on a group of healthy volunteers, this has not been the case.^{9,15,16} Instead, patients referred for imaging with a pretest low likelihood of coronary disease are used.

Normal volunteers are not used for several reasons. First, it is difficult to convince healthy volunteers to undergo exercise ²⁰¹Tl testing. Second, using low-likelihood patients provides age-matched controls; healthy volunteers are usually much younger than the typical patient with coronary artery disease.

Patients who have undergone coronary angiography and have been shown to have normal coronary arteries are also not used for normal files.¹⁶ Studies have indicated that these patients may not be a good reflection of "normal" (see Results for a further discussion of the problems surrounding these patients).

Patients are chosen for inclusion in the normal files by sequential Bayesian analysis of the probability of having coronary artery disease before a ²⁰¹Tl study is performed. The analysis is based on age, sex, symptom classification, and results of a stress electrocardiogram.⁹ Additional tests, such as fluoroscopic examination

for coronary artery calcification, are sometimes used as well.^{15,16} A probability of coronary artery disease is determined based on published tables or computer programs. Patients with less than a 1%¹⁵ or 3%⁹ probability of coronary artery disease are used.

The anatomic location of the segment with the highest number of counts varies among normal subjects. For this reason, the data are pooled to obtain a mean and standard deviation of activity in each segment.⁹ Separate databases must be used for each view. The lower limit of normal is as low as 45% below the maximum at the apex on the 45° LAO view to as high as 20% below maximum in the inferior wall on the anterior view.¹⁵

A recent discovery has marked the need for gender-matched normal files. Rabinovitch et al showed decreased anterior and upper septal wall uptake in women.¹⁸ The difference between sexes in the anterior wall is caused by breast attenuation. The upper septal wall decrease is likely a combination of breast attenuation and smaller left ventricular size in women. Because even gender-matched normal databases do not take into account the marked variation in breast size and shape, they will still misidentify some female patients as abnormal because of significant soft tissue attenuation.

The normal databases used by these programs are not large. Garcia et al have 31 to 49 patients in their normal patient database.^{15,16}

Results

The results of quantitative analysis are usually based on both circumferential profiles and washout data (see Washout Profiles below). Garcia et al, in their initial study, reported a sensitivity of 95% using quantitative analysis in a group of 20 patients with coronary artery disease.¹⁵ Specificity was 100% in 31 normals. Eleven patients and 6 normals underwent studies processed by two different computer operators to assess reproducibility of the technique. Concordant results were found in 93 of 99 segments. In the six segments in which there was discordance, the problem was a slight variation in aligning the apex at 90° in patients with large apical defects.

In a multi-institutional study of this program involving four institutions and more than 150

patients, the overall sensitivity for coronary artery disease was 84%.¹⁶ The correct identification of multivessel disease occurred in 71% of cases. The specificity for the absence of multivessel disease was 57%. Not surprisingly, the sensitivity improved with the number of diseased vessels. Sensitivity was 73% for detecting coronary artery disease in single-vessel disease, 87% in double-vessel disease, and 94% in triple-vessel disease. Sensitivities and specificities varied dramatically by vessel. The right coronary artery had the highest sensitivity with 89%; the left anterior descending coronary artery was next with 75%. Disease involving the circumflex artery was detected in only 41% of cases. These sensitivities differ somewhat from visual readings in which disease involving the left anterior descending artery is detected best. As with the quantitative program, visual review is least sensitive for circumflex artery disease.¹⁹ Specificity was 47% for the right coronary artery, 67% for the left anterior descending artery, and 80% for the circumflex artery.¹⁶

There are several explanations for the differences in sensitivity and specificity between vessels. First, with planar imaging the circumflex distribution is examined en face and on only one view, whereas the right coronary and left anterior descending artery distributions are seen from a perpendicular viewpoint on several views. This probably reduces sensitivity for the circumflex distribution. Specificity is improved, however, because there is little overlap with other vascular distributions. Second, in all three views the widest range between the mean and lower limit of normal occurs in the region of the circumflex artery on the 45° view. This lower threshold for abnormality reduces sensitivity but increases specificity.¹⁶

Rather than expressing the results of these quantitative programs in terms of overall specificity (true-negatives/[true-negatives + false-positives]), Garcia et al have chosen to use the normalcy rate. This is an expression of how frequently a test can correctly exclude disease in a subpopulation of patients with a low likelihood of coronary artery disease, less than 5% (see Normal File above). A normalcy rate of 88% was found using the quantitative program of Garcia et al.

The specificity of a positive quantitative ²⁰¹Tl

scan in patients with normal coronary arteries on coronary angiography is only 50%. Why the discrepancy? The primary reason is posttest referral bias.¹⁶ With ²⁰¹Tl scanning, patients with normal results of examinations are considered unlikely to have coronary artery disease, and even if they do, they are felt to have a good prognosis. For this reason, patients with negative results of ²⁰¹Tl examination are preferentially selected not to undergo coronary angiography. In contrast, patients with positive ²⁰¹Tl study results are preferentially sent for catheterization. With this referral bias, and using the coronary angiogram as the gold standard, the apparent specificity will be far lower than the true specificity of the test if it were measured in an unbiased population. In fact, if only patients with positive test results were catheterized, this referral bias would in theory lead to a 100% test sensitivity and 0% specificity, regardless of the true sensitivity and specificity of the test. Studies have confirmed the apparent lowering of specificity of other tests with time because of referral bias, most notably the exercise radionuclide ventriculogram, which has had reported specificities as low as 21%.¹⁶

There are a number of explanations for the substantial portion of patients with angiographically normal coronary arteries but abnormal results of quantitative ²⁰¹Tl scans. Some are caused by technical difficulties in quantitating ²⁰¹Tl uptake. The effects of attenuation may play a large role. Women with large breasts and men with thick chests will attenuate the low-energy photons of ²⁰¹Tl to a greater degree than patients who are more slender. This can result in lower count rates being measured. But many physicians feel that most patients with abnormal quantitative ²⁰¹Tl scan results have a true perfusion defect. Vogel et al found perfusion abnormalities using digital-subtraction coronary angiography in 100% of the patients with abnormal results of ²⁰¹Tl scans and normal results of conventional coronary angiograms.²⁰ A high degree of interobserver variability has been reported in the visual interpretation of coronary angiograms, which may explain some of these cases.²¹⁻²³ Diffuse atherosclerosis, eccentric lesions, small vessel disease, exercise-induced coronary artery spasm, and occult cardiomyopathy also contribute to the discrepancies between

results of coronary angiography and ²⁰¹Tl scans.²⁴⁻²⁹

Wackers et al have compared the results of their quantitative program with those of visual analysis.⁹ They performed ²⁰¹Tl imaging on 150 patients with possible coronary disease; all underwent coronary angiography for confirmation of the diagnosis. Significant coronary stenosis, defined as narrowing of greater than 70%, was present in 131 patients. Nineteen had angiographically normal coronary arteries.

Eight-five of 131 patients with coronary artery disease were correctly identified by visual review of the unenhanced analog images. Quantitative analysis, on the other hand, detected coronary artery disease in 117 patients. Of the 19 normal patients, all were correctly categorized by visual review, whereas in 1 normal subject coronary artery disease was incorrectly diagnosed by quantitative analysis. This yields a sensitivity of 65% using visual analysis compared with 95% using quantitative analysis. Overall specificity was 100% using visual analysis and 95% using quantitative analysis. The positive predictive accuracy of a positive ²⁰¹Tl scan results was 100% using visual review of the images and 99% with quantitative analysis.

The sensitivity of CAID for coronary artery disease was most markedly increased over visual analysis of patients with single-vessel disease. In these patients, the sensitivity using visual review was only 55% compared with 84% using quantitative analysis. However, quantitative analysis improved sensitivity for multivessel disease as well; double- and triple-vessel disease were detected using visual inspection in 79% and 80%, respectively, compared with 94% and 100% using quantitative analysis. As these figures indicate, most incidences of disease that were missed by quantitative analysis were in patients with single-vessel disease.

The predictive accuracy of the technique for localizing disease to a specific vessel was also measured. The accuracy was 82% for the left anterior descending artery, 60% for the right coronary artery, 36% for the left circumflex artery, and 74% for the combination of either the right coronary or the circumflex artery. These figures are suboptimal but were better than those obtained with visual analysis. The

Table 5. Summary of Circumferential Profile Results for Overall Detection of Coronary Artery Disease

	Sensitivity	Specificity
Garcia et al	95%	100%
Multi-inst Trial	84%	88%*
Wackers et al	95%	95%

*Normalcy rate.

overall results of this study and that of Garcia et al are summarized in Tables 5 and 6.

Determining Reversibility and Severity

The number, extent, severity, and reversibility of ^{201}Tl perfusion defects correlates with the clinical severity of coronary artery disease and with the risk for future cardiac events.³⁰ Quantitative analysis can determine the severity of a lesion and whether it represents ischemia or infarct. Using data from the circumferential profile, the size of the myocardial perfusion defect is determined by integrating the area of the profile curve under the lower-limit-of-normal line. The area obtained represents the amount of hypoperfused myocardium.³⁰ An example is shown in Fig 4. The area is expressed as a proportion of the total potentially normal myocardium. This value, called the defect integral, is unitless and represents both the extent and severity of the perfusion abnormality. It has been shown that the defect integral increases as the visually graded severity of a perfusion defect increases.³¹

In addition to severity of a perfusion defect, the defect integral can be used to differentiate ischemia from infarct by comparing the defect integral at stress with the same area's integral score at redistribution. If the score changes significantly, some degree of ischemia is present.

To determine what a significant change in the defect integral score is, computer operators processed the same images repeatedly. They found the mean absolute intraobserver difference in the defect integral for exercise studies was 1.5 ± 1.9 . Expressed as a percentage of defect size, this is $20\% \pm 36\%$. Larger defects

Table 6. Sensitivity of Circumferential Profiles for Detecting Coronary Artery Disease by Number of Diseased Vessels

	1	2	3
Multi-institutional trial	73%	87%	94%
Wackers et al	84%	94%	100%

Fig 4. Method for calculating the defect integral (Reprinted with permission.³⁰)

(defect integral, >5) had less variation on repeat processing than small defects (defect integral, 1 to 5).

Rather than using comparisons with human expert readings to develop criteria for reversibility, the calculated intraobserver variability is used. Thus, a study is considered to show definite ischemia if the defect integral changes more than 2 SD greater than the mean variability. Changes of between 1 and 2 SD are considered probable ischemia, and changes of less than 1 SD represent an infarct.

Because variability (expressed as a percentage of defect size) is less in larger defects, adjustments for lesion size are made in the criteria for reversibility. In small lesions (defect integral, 1 to 5), a minimum change in integral score of 2 is required, which represents a 70% relative difference between stress and redistribution. However, large defects (defect integral, >15) only need a change in score of 6, a 27% relative difference, to indicate ischemia.

Unfortunately, there is no noninvasive gold standard for determining reversibility of ^{201}Tl perfusion abnormalities. Comparison with human experts found concordance in 82 of 105

images (78%) and a κ statistic (a measure of agreement varying from 0 to 1) of 0.66. Much of the disagreement involved small defects (defect integral of 2 or less) in which the quantitative program could not differentiate between statistical noise and true reversibility. In these cases, the program falsely diagnosed abnormalities. The other source of error involved moderate-sized defects in which human observers diagnosed reversibility, but the program found the changes between stress and redistribution to be less than 1 SD. These were incorrectly called infarcts rather than ischemia.

WASHOUT PROFILES

Washout profiles represent the percentage of ^{201}Tl that clears from a myocardial segment during the 2 to 4 hours between stress and redistribution imaging. The degree of change is usually lesser in ischemic tissue. Washout profiles offer the possibility of diagnosing coronary disease that is not appreciated on visual reading because relative changes in activity over time cannot be accurately evaluated by unaided human observers.⁹

The initial uptake of ^{201}Tl into myocardial tissue is primarily dependent on blood flow.³² The washout of ^{201}Tl is a complex phenomenon that is dependent on the net effect of two opposing cellular processes, the extraction of ^{201}Tl from the blood versus the efflux of ionic thallium from the cells. The cellular basis for the uptake of ^{201}Tl is not completely understood. Many investigators feel that thallium is a potassium analogue and that the sodium-potassium pump is responsible for cellular extraction.³³⁻³⁵ However, other investigators have reported a passive transport mechanism that is controlled by the electropotential gradient across the cell membrane.^{33,36,37} In cell cultures of fetal heart tissue, the extraction rate of ^{201}Tl is not affected by reduced flow until levels producing irreversible damage are reached.³⁸ Similarly, hypoxia has been shown not to affect the extraction rate.³⁹ Thus, ischemic cells continue to extract ^{201}Tl at normal rates.

The factors affecting the release of ^{201}Tl from myocardial cells has also been studied. Okada et al have measured the kinetics of ^{201}Tl in normal canine myocardium by implanting, in living dogs, miniature cadmium telluride radia-

tion detectors positioned against the left ventricular endocardium.³³ They found that early, the myocardial cells accumulate more thallium than they release, resulting in a net increase in intracellular levels of ^{201}Tl . The time for reaching the peak ^{201}Tl concentration was dependent on two factors: blood flow to the region and the concentration of ^{201}Tl in the blood. After peak activity, the thallium begins to wash out of the myocardium. The rate of clearance of ^{201}Tl from the myocardial cells is primarily related to the rate of ^{201}Tl clearance from the blood. In these normal dogs, the mean time to peak was 24 minutes; myocardial clearance (washout) was monoexponential with a decay constant of 0.00176 min^{-1} and a half-life of 7.3 hours.³³

By placing a balloon occluder in the distal left anterior descending artery, Okada et al have also studied the effect of ischemia on myocardial clearance of ^{201}Tl .⁴⁰ They found ischemia caused a lower peak of ^{201}Tl uptake, a delayed time to peak of 40 to 90 minutes, and a lower decay constant. These factors resulted in lower net myocardial clearance at 4 hours. Of the three factors, the delayed time to peak may be the most important.^{39,40} The cells in the underperfused zone are exposed to a lower net amount of ^{201}Tl early and must continue to extract the tracer from the very low level in the blood until they achieve the peak. They then begin to release ^{201}Tl , although at a slower rate than normal.³⁹

The delay in washout is directly related to the degree of ischemia.^{40,41} Thirty-five percent of the ^{201}Tl washed out of normal dog myocardium over a 4-hour period. Values as low as 5% occurred in animals with severe stenoses (see Table 7). Animals with severe reductions in flow associated with necrosis had clearance curves close to those corresponding to findings in normal regions of myocardium.^{40,41}

Table 7. ^{201}Tl Kinetics in Dogs

	Time to Peak (min)	Decay Constant	Clearance (%)
Normal	4.4	0.0016	35
Mild stenosis	9.5	0.0011	27
Moderate stenosis	11.0	0.0006	19
Severe Stenosis	83	None	5

Technique

The technique for calculating washout is simple. Washout is the percentage of activity in a myocardial segment that clears between stress and redistribution.^{15,16} It is expressed mathematically as a percentage: $[(\text{stress activity} - \text{redistribution activity}) / \text{stress activity}] \times 100$ (Fig 5).

As discussed in Circumferential Profiles above, Garcia et al divide the ventricle into 6° segments. Each segment must be 2.5 SD less than the mean to be considered abnormal. A total of three contiguous segments (18° arc) must be abnormal. This group combines the results of the circumferential profile with the washout profile to make a final diagnosis of coronary artery disease. At least two 18° arcs must be abnormal in the two profiles for a positive scan.

Wackers et al divides the ventricle into 10° segments.⁹ Each segment must be 2 SD below the mean. A total of five contiguous segments (50° arc) must be abnormal to diagnose coronary artery disease (Fig 6).

Because the time between the stress and redistribution images may vary, some investigators interpolate the normal washout profiles from 4 hours to the actual time used based on a $T_{1/2}$ of 12.4 hours between 3 and 6 hours postinjection.^{15,16} Other investigators feel that the time of imaging is too critical to vary (see below).

Fig 5. Normal washout profile. Capital letters at the top indicate segments. The left side of the chart shows counts, the right the percent washout. Black dots represent stress, white dots redistribution. The lower limit of normal for washout is shown as a solid black line. The gray bars at the bottom of the graph represent the percentage of washout in each 10° arc.

Fig 6. Washout profile of a patient with extensive coronary artery disease. Both infarct and ischemia are present. Note abnormal washout at edges of graph. Infarcted tissue in middle segments shows little change between stress and redistribution.

Conventional washout techniques only use the walls that are tangential to the camera; the myocardium that is en face to the camera is not evaluated.⁴² To overcome this deficiency, a parametric color-coded washout image can be generated. These images are produced from the regional washout values calculated from filtered, background-subtracted, superimposed stress and redistribution images. The regional washout percentage is mapped using 64 colors. Each pixel is intensity-coded according to the relative value derived from a vectorial sum of plotted counts in the postexercise and redistribution images, preserving visibility of the region of the apparent cavity and any fixed abnormalities in the washout image.⁴² All images are reprocessed to extrapolate to 4 hours based on monoexponential clearance.

The technical factors involved in acquiring images used for washout profiles are extremely important. Potential problems are summarized in Table 8.

The first problem is the timing of the stress and redistribution scans. Some investigators

Table 8. Technical Factors That Can Adversely Affect the Washout Profile

Delayed stress and redistribution scans
Low count rates
Reangulation errors between stress and redistribution imaging
Submaximal exercise
Arm vein uptake

have recommended delaying the initial scan when quantitative analysis is performed.⁹ They argue that the initial myocardial activity measured in the first 8 minutes includes a large contribution from ²⁰¹Tl in the blood. This results in measured myocardial levels that are falsely elevated, which may cause the difference in stress and redistribution counts to appear normal when the actual washout is below normal. ²⁰¹Tl concentration in the blood shows a rapid decrease in the first 7 minutes after injection. However, Wackers et al have shown that in spite of the significant change in blood ²⁰¹Tl counts, the background-corrected myocardial activity is approximately constant over this time.⁹ Because blood-pool activity is low compared with myocardial activity, it is likely to have little effect. The linearity may also be caused by a flat net result of myocardial accumulation versus blood clearance.

Advantages of immediate imaging can be seen in the variable washout curves of normals and patients with coronary artery disease. Although a net washout of ²⁰¹Tl occurs in almost all patients, the initial direction of change (increase, decrease, or flat) is extremely variable. If the initial scan is delayed, both false-positive and false-negative results can occur.

The timing of the delayed scan is also important. The classical time for performing redistribution imaging is 4 hours. However, this may be too delayed for washout analysis. ²⁰¹Tl clearance is variable and, according to Wackers et al, appears to be approximately linear in clinical patients (this is at odds with the monoexponential disappearance curves measured in animals).⁹ Imaging at 2 hours results in higher count rates that improve the quality of the study (see below). The washout rate decreases both in normal and in transiently ischemic myocardium with the interval from thallium injection. Initial differences in washout become less distinct if delayed measurements are used.

Low count rates have been shown to cause false-positive and false-negative results. In a phantom study of background-subtracted left ventricular areas of interest, it was found that as the count densities decreased, bizarre and erratic washout values occurred in all zones.⁹ Many of these were false-positives. The study found that the reliability of washout analysis

improved considerably when the counts in a segment exceeded 910. This corresponded to a mean count per pixel of 37 and a maximal count per segment of 40/pixel. These numbers translate into a minimum requirement of 33,000 counts in the left ventricular region of interest after background subtraction. To obtain these count densities, a total count rate of at least 400,000 in the entire field is necessary. Why not obtain as high a count rate as possible? Because ²⁰¹Tl is washing out with time. The imaging time should not be so long as to reduce temporal resolution. Wackers et al recommend 8-minute images that typically yield images with 600,000 counts.⁹

Low count rates after background subtraction in zones of infarction (which have little ²⁰¹Tl activity) have been shown to cause falsely fast washout rates in some patients.^{41,43} This phenomenon tends to occur when the ratio of activity between the normal and abnormal myocardium is 6:1 or less. The low count rates found in peri-infarction tissue can lead to inaccurate diagnoses of peri-infarction ischemia by washout analysis.⁹

Differences in camera repositioning between stress and redistribution images can also reduce the accuracy of washout analysis. Phantom studies have shown that when the camera is tilted 5° to 20° from the true angle between stress and redistribution, a false increase in percent washout occurs in the wall of the phantom that is tilted toward the camera surface, with a false decrease on the opposite side that is tilted away from the camera.⁴⁴ This occurs because the volume of activity is greater on the side the camera is tilted toward and reduced on the opposite side. Thus, both false-positive and false-negative washout profiles can be produced. The effect becomes more pronounced as the angle of misalignment increases.

The level of exercise is another critical factor for washout studies. Massie et al found that submaximal exercise leads to decreased washout rates that can be incorrectly classified as ischemia.⁴⁵ The 3-hour washout rate in normals and patients who did not reach 85% of their age-predicted maximal heart rate was 25% compared with 38% in individuals who reached maximum exercise. The effect of heart rate is linear; for each 1 beat per minute below the

maximum, ^{201}Tl clearance is slowed by 0.05 hours.⁴⁶ Using this figure, investigators have found they can correct washout values in patients who submaximally exercise.

Why is ^{201}Tl washout slower with submaximal exercise? The main determinant of myocardial ^{201}Tl uptake is the amount of thallium delivered to the heart which, in turn, is proportional to the ^{201}Tl concentration in the blood and the coronary blood flow.^{45,46} Coronary blood flow is dependent on the level of exercise (and heart rate obtained). Therefore, the higher the heart rate, the more ^{201}Tl extracted by myocardial tissue. As discussed earlier, the washout kinetics of thallium are related to the difference between the myocardial and blood concentrations of ^{201}Tl . With a higher initial concentration of ^{201}Tl in the heart, the washout will be faster.

A final factor that can affect washout rates is the vein used to inject the thallium. When ^{201}Tl is injected in veins other than the medial antecubital vein, thallium uptake is seen proximal to the injection site in 53% of patients.⁴⁷ These patients have 33% lower net myocardial counts in the immediate poststress images and 20% fewer counts in the delayed views. The washout rates are also slowed; in this study washout was 48% over 4 hours in those without arm vein uptake but only 36% in those with it. Because washout appeared slowest in individuals whose arm uptake completely cleared by the time of the delayed images, it was postulated that the measured delay in washout was because of the slow, constant infusion of thallium into the blood from the arm during the redistribution period. These slower washout rates reflected the diminished ^{201}Tl concentration differences between the blood and myocardium.

Normal Files

Normal values for washout profiles are generated from the same population used for circumferential profiles. Therefore, the same considerations that were discussed earlier apply to these studies.

Unlike circumferential profiles, which show a significant variation in maximum counts in different regions of the heart, washout profiles are much more homogeneous. This allows a small range of washout to be used as the normal value

for all the heart walls.⁹ Reported normal values have averaged from approximately 30% to as high as 65%.^{9,18,42}

As with circumferential profiles, there are sex differences in the rate of washout.¹⁸ In a comparison of 23 men and 26 women with a less than 2.5% chance of coronary artery disease, men averaged a 57% washout rate compared with 65% for women.

The reasons for these differences are not known. It seems unlikely that monovalent cation cellular kinetics would differ in men and women.¹⁸ The men in the current study reached a slightly higher mean peak exercise heart rate in the above study. If higher levels of myocardial blood flow were the cause, men rather than women would have been expected to have had the faster washout rate. Breast attenuation has also been considered.¹⁸ However, the degree of attenuation should be the same at both stress and redistribution unless there is some shifting of the breast position at the two imaging times. Therefore, the net difference in counts between stress and redistribution should not be affected. In addition to theoretical arguments, studies have shown that women with fast washout rates do not have larger breasts than other women in the study.¹⁸ In fact, fast washout has been observed in women with small breasts. Finally, more rapid washout has been found in the inferior myocardial segments of women than the inferior region in men. Breast attenuation should not significantly affect this region.

Results

The exact sensitivity and specificity of washout profiles are not easy to ascertain because many investigators report results for combined circumferential profile and washout analysis without giving data about the individual contributions of each.^{9,16} However, some groups report increased sensitivity for disease using washout analysis without providing exact figures.^{9,12,15}

Maddahi et al studied a pilot group of 31 normals and 20 patients with coronary artery disease to develop normal files for their circumferential profile (discussed earlier under Garcia et al) and washout profile.⁴⁸ They then compared their quantitative technique with visual analysis in 22 normals and 45 patients with coronary artery disease. Using both circumferen-

tial and washout profiles, the sensitivity and specificity were similar to those for visual analysis (93% and 91% sensitivity and specificity, respectively, for the quantitative technique, compared with 91% and 86% for visual analysis). However, of 110 cardiac regions supplied by diseased vessels, 35 were missed visually. Of these, 54% were detected on the basis of washout alone. In 23%, both washout and circumferential profiles were abnormal. In the remaining 23%, the abnormality was seen only on circumferential profile. Interestingly, in 15 of the 19 regions detected only by washout analysis, the other vascular regions on that view were supplied by vessels that had luminal narrowing equal to or greater than that in the segment showing isolated slow washout.

In 91 regions supplied by normal vessels, 7 were falsely positive by quantitation. Two had diffuse slow washout, 3 had a combination of washout and circumferential profile abnormalities, and 2 were abnormal on circumferential profile alone.

Maddahi et al have also reported on using diffuse slow washout as an indicator of severe coronary artery disease.⁴⁹ Identifying these patients is important because triple-vessel and left main coronary artery disease are known to result in increased morbidity and mortality. Attempts to identify these patients by visual analysis alone have been disappointing.⁵⁰

These investigators analyzed 1,265 cases and found 46 with diffuse slow washout and no or only one regional perfusion defect. Seventy-three percent of these cases had triple-vessel or left main coronary artery disease. In 30 similar patients without diffuse slow washout and no or one perfusion defect, only 5% had extensive coronary artery disease. Nine of the patients with high-risk anatomy had entirely normal scans visually, and another 14 had defects suggestive of only one diseased vessel.

Visual analysis and quantitative analysis that depends on comparison with a normal segment can miss cases of triple-vessel disease, because the initial distribution of ²⁰¹Tl depends on relative rather than absolute differences in blood

Table 9. Sensitivity of Washout Profiles for Coronary Artery Disease

	Visual Analysis	Quantitative Analysis
Maddahi et al	91%	93%
Botvinick et al	61%	93%

flow. If all segments have decreased flow, they will appear homogeneous on a set of images. Similarly, if all three vessels are abnormal but one is more severely stenotic than the other two, it will appear as if there is only one defect.⁴⁹

Interestingly, this group found that the predictive accuracy of the washout profile was not affected by submaximal exercise. They suggest that the development of diffuse washout abnormalities is less affected by exercise level than are focal washout abnormalities.

Botvinick et al used their parametric color-coded images to evaluate washout in 25 patients.⁴² The sensitivity of visual analysis for regions of coronary artery disease confirmed by cardiac catheterization was only 61% compared with 93% using washout analysis. The number of false-positives was reduced as well. Visual analysis yielded five false-positives in a group of normals whereas the parametric washout technique had no false-positives. Table 9 summarizes the results of washout analysis.

CONCLUSION

Quantitative analysis is a useful aid to the interpretation of ²⁰¹Tl-perfusion scans. However, the technique requires extreme attention to detail.

In a future article we will examine the use of computer-assisted diagnosis for single-photon-emission CT (SPECT). The techniques used for evaluating SPECT studies are an outgrowth of the planar programs. We will also discuss quantitation of pharmacological stress studies and perfusion studies performed with new radiopharmaceuticals such as the technetium isonitriles. We will include a discussion of advanced image-interpretation techniques using three-dimensional renderings, expert systems, and neural networks.

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