Assessment of Coronary Artery Disease Severity by Positron Emission Tomography
Comparison With Quantitative Arteriography in 193 Patients

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To assess the accuracy of positron emission tomography (PET) for evaluation of coronary artery disease (CAD), cardiac PET perfusion images were obtained at rest and with dipyridamole-handgrip stress in 193 patients undergoing coronary arteriography. PET images were reviewed by two independent readers blinded to clinical data. Subjective defect severity scores were assigned to each myocardial region on a 0 (normal) to 5 (severe) scale. Results were compared with arteriographic stenosis severity expressed as stenosis flow reserve (SFR), with continuous values ranging from 0 (total occlusion) to 5 (normal), calculated from quantitative arteriographic dimensions using automated detection of the vessel borders. There were 115 patients with significant CAD (SFR<3), 37 patients with mild CAD (3≤SFR<4), and 41 patients with essentially normal coronaries (SFR≥4). With increasingly severe impairment of stenosis flow reserve, subjective PET defect severity increased. Despite wide scatter, a PET score of 2 or more was highly predictive of significant flow reserve impairment (SFR<3). For each patient, the score of the most severe PET defect correlated with the SFR of that patient’s most severe stenosis (r=0.77±0.06). For each of 243 stenoses, PET defect score correlated with the SFR of the corresponding artery (r=0.63±0.08). PET defect location closely matched the region supplied by the diseased artery, and readers agreed whether the most severe PET defect was less than or more than 2 for 89% of patients. (Circulation 1989;79:825-835)

Myocardial perfusion imaging is widely used for noninvasive assessment of stenosis severity. Knowledge of the diagnostic accuracy of these tests is important for proper clinical application and interpretation. Most previous reports of the diagnostic accuracy of myocardial perfusion imaging1-4 have used sensitivity-specificity analysis to describe the relation between image defects and arteriographic disease. This method requires binary (positive or negative) classification of both imaging and arteriographic results. Arteriographic results have usually been described in terms of percent diameter narrowing, with a threshold value of 50% as the criterion for presence of coronary disease.

There are three limitations to this use of sensitivity-specificity analysis for assessing accuracy of noninvasive tests for coronary disease. First, coronary disease is not an all-or-none condition; binary classification requires arbitrary threshold criteria and creates artificial distinctions in coronary artery disease that, in actuality, has a continuous spectrum of severity.

Threshold values that yield optimal sensitivity and specificity values for one test may yield falsely lower values for a different but more accurate test if its detection threshold is different. For example, an imaging test capable of detecting 40% stenoses may have low specificity according to a 50% stenosis
criterion but high specificity according a 40% stenosis criterion.

Second, sensitivity and specificity values are also determined by the disease distribution of the study population. A sample population with a high frequency of mild disease will be distributed centrally near the threshold values where scatter is more likely to lower sensitivity and specificity. The sensitivity and specificity found in one population may not apply to a different population. To overcome these limitations, analysis of test results as continuous variables has been proposed.

Finally, recent reports by Marcus and others have indicated that percent diameter narrowing is not an adequate standard for quantifying stenosis severity in clinical studies. It does not account for the effects of diffuse disease, inherent eccentricity, stenosis length, viscosity, cross-sectional area, entrance and exit angles, and absolute dimensions on flow impedance; and it is limited by substantial interobserver and intraobserver variability. Proposed alternative approaches include quantitative arteriographic methods based on the Brown-Dodge method to calculate stenosis flow reserve and direct measurement of coronary flow velocity by Doppler catheter.

In an earlier study, Wijns and colleagues used quantitative arteriographic and direct physiologic measurements to assess the accuracy of planar PET imaging, but they retained the conventional threshold criteria to classify arteriographic severity and perfusion defect severity as positive or negative. The feasibility of clinical PET perfusion imaging has also been addressed in previous work by Schelbert and colleagues and, with quantitative arteriographic flow reserve, by our group. These studies also retained the binary classification system and involved smaller numbers of patients.

The purpose of the present study was to reevaluate the accuracy of positron perfusion imaging in assessment of coronary disease severity with scales covering the range of disease severity rather than binary classification, direct correlation rather than sensitivity-specificity analysis, and quantitative arteriographic flow reserve rather than percent diameter narrowing, in a large series of patients.

Methods

Study Patients

Subjects consisted of 193 patients (143 men, 50 women) undergoing diagnostic cardiac catheterization. The patient sample included 50 patients previously reported in a study where binary classification and sensitivity-specificity analysis were used. Clinical indications for arteriography included chest pain syndromes, myocardial infarction, abnormal stress tests, coronary angioplasty, thrombolytic therapy for acute infarction, evaluation before renal transplant, before and after cholesterol lowering programs, or as part of screening feasibility studies.

Sixty-six patients were clinically diagnosed as having a previous myocardial infarction. From an initial group of 209 patients, 12 early patients were excluded because part of the heart was not imaged due to positioning error, and four PET images were not interpretable due to camera or computer malfunction. Patients were not enrolled if there was evidence of unstable angina or active bronchospasm with theophylline bronchodilator therapy, which are contraindications to intravenous dipyridamole. After informed consent was obtained, coronary arteriography and PET imaging were performed according to protocols approved by the University of Texas Committee for Protection of Human Subjects.

Quantitative Arteriography

Cineangiographic frames of orthogonal views were digitized for each stenosis involving a major artery, including diagonal, obtuse marginal, ramus intermedii, and acute marginal branches. Absolute and relative stenosis dimensions were measured with a computer program providing automatic detection of vessel borders (Figure 1), with an accuracy of ±0.1 mm. The theory and equations for predicting stenosis flow reserve from these dimensions have been described previously. In brief, the coronary perfusion pressure distal to each stenosis was calculated as a function of flow according to the equation:

\[ P_{\text{cor}} = P_{A_o} - (fQ + sQ^2) \]

where \( P_{\text{cor}} \) is distal coronary pressure, \( P_{A_o} \) is aortic pressure, \( Q \) is flow, \( f \) is \( 8\mu rL/A_o^2 \), \( s \) is \( \rho ((1/A_o) - (1/A)) \), \( A_o \) is minimum absolute area, \( A \) is absolute area of normal adjacent artery, \( \mu \) is blood viscosity, \( \rho \) is blood density, and \( L \) is stenosis length.

This relation, shown as the curved line in Figure 1, lower panel, was compared with the known pressure-flow relation for conditions of maximal coronary vasodilation, shown as the diagonal line. Stenosis flow reserve (SFR) was defined as the intersection of these two relations (i.e., flow at maximum coronary vasodilation) relative to rest flow, under standardized hemodynamic conditions. In comparison with direct measurements by electromagnetic flow meter, the 95% confidence interval was ±0.66 with a reproducibility of 2–3%. The advantages of SFR over other methods of describing stenosis severity have been discussed in detail in a recent editorial. Coronary arteries were considered normal if patent bypass grafts supplied the arterial bed (two patients). Five patients having their PET study after acute myocardial infarction, with normal coronary arteriography after revascularization of chronic occlusions, were considered to have total occlusions for the purposes of patient-by-patient analysis. Infarct-related stenoses of 19 patients who had undergone acute revascularization were excluded from this analysis because the residual stenosis severity would not be comparable to the variable degree of resultant perfusion defect; the remaining stenoses in these patients were included in the regional analysis.
FIGURE 1. Top panel: Automated edge-detection analysis of a coronary arteriogram. Bottom panel: Quantitative arteriographic data for another patient including plots of diameter and cross-sectional lumen area as functions of axial position (lower left); parameters calculated from dimensions including minimal, proximal, distal, and percent diameter in each view (D₁, D₂), minimal, proximal, distal, and percent cross-sectional area, volume, length, and relative length of the stenosed segment, entrance and exit angles (α and Ω), predicted rest flow (Qᵢ), and viscous and expansion loss coefficients (Cᵥ, Cₑ, Kᵥ, Kₑ) (upper left); and the derived pressure-flow relation and stenosis flow reserve (upper right). The diagonal line crossing the pressure-flow curve represents the condition of maximal arteriolar vasodilation. As flow increases, pressure distal to the stenosis decreases, until it reaches a minimum at the point of maximal vasodilation. Stenosis flow reserve is defined as that maximum value of flow relative to resting flow (Q/Qᵢ) under standardized hemodynamic conditions, where normal stenosis flow reserve is 5.
FIGURE 2. Positron emission tomographic $^{82}$Rb images acquired from a patient with proximal disease of the left anterior descending artery before (top row of upper and lower images) and after (bottom row) intravenous dipyridamole with handgrip stress. The views are oriented in the oblique semi-long axis and arranged in vertical order from base (upper left) to inferior wall (lower right). Each slice is viewed from above so that the apex is at the top, the lateral free wall on the left, the valve ring at the bottom, and the interventricular septum at the upper right of the horseshoe-shaped left ventricular slices. In the color coding, white is the highest, red next highest, yellow intermediate, and green and blue lowest uptake. There is a large anterior, septal, and apical defect. The right ventricular wall is not normally visualized on PET imaging due to its thin walls.

**Positron Emission Tomography**

Patients were fasted for 4 hours, and caffeine and theophylline were withheld for 8 hours before imaging to prevent interference with the hyperemic effect of dipyridamole. Fluoroscopy was used to mark the cardiac borders for proper patient positioning. Scans were performed with the University of Texas multislice tomograph$^{17,22}$ with a reconstructed resolution of 14 mm full-width half-maximum. Transmission images were performed to correct for photon attenuation. Emission images were obtained with $^{82}$Rb produced by a portable generator$^{23}$ or, when $^{82}$Rb was not available, $^{13}$N ammonia.$^{17,24,25}$ Eighty-two patients received $^{82}$Rb and 111 received $^{13}$N ammonia. The tracer was injected through a 20-gauge catheter inserted into an antecubital vein. To allow for blood pool clearance, there was a 1-minute delay after $^{82}$Rb and a 3-minute delay after ammonia administration. After this delay, data were acquired for 5–8 minutes for $^{82}$Rb and 15–20 minutes for $^{13}$N ammonia. After isotope decay, 10 minutes after administration of the first dose of $^{82}$Rb or 40 minutes after $^{13}$N ammonia, dipyridamole (0.142 mg/kg/min) was infused for 4 minutes. Two minutes after the infusion was completed, 25% of the predetermined maximal handgrip was begun as described by Brown.$^{26}$

At 8 minutes from onset of the infusion, a second dose of the same amount of the same tracer was injected, and imaging was repeated. Data were acquired over the same period. Radiation doses involved in these procedures have been described previously.$^{27-29}$ For those patients developing significant angina, aminophylline (125 mg) was given intravenously.
Image Interpretation

As previously described,17 rest and stress images with nine tomographic slices each, were displayed in an isocount color format. This format consisted of five primary colors (white, red, yellow, green, and blue) in order of highest to lowest counts, each divided into 3% gradations of shade. Images were visually interpreted by two independent readers (KLG, RAG) blinded to clinical data. In two cases, only one interpretation was available due to loss of data files. Rest and stress images were displayed either side-by-side or superimposed with adjustable color scales (Figure 2).

Seven regions of each cardiac image (anterior, apical, anteroseptal, posteroseptal, anterolateral, posterolateral, and inferior walls) were evaluated. Perfusion defects, defined as regions of subjectively lower counts in at least two contiguous slices compared to the remainder of the heart, were graded on a 0 to 5 scale defined as normal (0), possible (1), probable (2), mild (3), moderate (4), and severe (5) defects, respectively. One score was assigned to each region. Each step of the scale corresponded to approximately one primary color step. For example, in general, a red region adjacent to a white region was not considered a definite defect; however, yellow adjacent to white was considered a definite defect. Relative size of the defect was also included in assigning the scale to allow for pixel noise. The average of the two readings was taken for each region, in effect resulting in an 11-point scale (0 through 5 in 0.5 increments) of PET defect severity.

Interobserver Differences in PET Scan Interpretation

PET defect scores assigned to each region by the two readers were compared for variability according to the criteria shown in Table 2. A similar method has been used to assess interobserver differences in interpretation of thallium perfusion images.29 Due to overlap of some portions of the seven cardiac regions defined above, minor differences in the description of regions contiguous to a large defect were allowed. For example, if a defect were described by one reader as having a grade 4 defect in the anterior, apical, and anteroseptal regions and 0 in the anterolateral region, whereas the other reader assigned a score of 4 to all four regions, then the readings were considered in essential agreement despite the difference in scores for the anterolateral region.

In eight cases, the qualitative interpretations differed markedly, and the readings were repeated independently. On repeat reading, the interpretations remained in disagreement except in two cases. The new readings were used for these two patients. For the other six, a mean of the divergent scores was used, as for the remaining patients.

## Table 1. Relation of PET Defect Location to Stenosed Coronary Artery in One-Vessel Disease

<table>
<thead>
<tr>
<th>Location</th>
<th>LAD-diagonal</th>
<th>Anterior</th>
<th>Anterolateral-anterosptal</th>
<th>Anterior and inferior</th>
<th>Anterosptal and posterolateral</th>
<th>None</th>
<th>SFR &gt; 3</th>
<th>SFR &lt; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right coronary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Inferior</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferolateral</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferoapical-apical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferoseptal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterolateral</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
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<td>SFR &gt; 3</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SFR &lt; 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; SFR, stenosis flow reserve.

Comparison of PET defect location with site of coronary artery narrowing for patients with one-vessel disease with SFR < 4.

Analysis

To determine the relation of PET defect severity to stenosis flow reserve, two analyses were used. First, the PET defect score was compared with its presumed corresponding artery for each defect-stenosis pair. Only the most severe stenosis was considered for each artery, and patients with neither stenoses nor PET defects were counted as only a single data pair rather than three pairs to prevent overweighting the extreme normal end of the scale. The anterior, septal, and anterolateral regions were associated with the LAD; the posterolateral region was associated with the circumflex; and the infero-posterior region was associated with the right coronary artery. Diagonal and ramus intermedius branches were associated with the same region as the LAD.

Second, because it may be difficult to determine with absolute certainty which artery corresponds to a given region, the data were also analyzed by comparing the most severe PET defect with the most severe SFR for each patient. The nonparametric rank correlation coefficients, standard errors, and confidence intervals were determined by the Spearman method and reported as the Spearman correlation coefficient, \( r_s \), \( \pm \) two times the SEE. Least-squares method was used to calculate the regression coefficients. Fisher's exact test was used to compare results of the two perfusion tracers.
Results

Coronary Arteriography

Coronary artery stenoses with flow reserve values less than 4 were found in 137 patients. Thirty-seven of these patients had stenosis flow reserve values between 3 and 4, consistent with mild disease. Fifteen had myocardial infarction with revascularization. Occlusive disease was present in 34, involving 42 vessels.

PET Defect Severity Versus Stenosis Severity for Each Artery

For the 243 stenosis-defect pairs among the 193 patients, PET defect score was compared with arteriographic severity of the corresponding coronary stenosis (Figure 3, top). With increasing impairment of flow reserve, subjective PET defective severity increases. Although there is wide scatter, a PET defect score of 2 or more, indicated by the vertical line in Figure 3, top, is highly predictive of significant flow reserve impairment (SFR < 3). PET score rank correlated significantly with SFR (r = 0.63 ± 0.08). Linear regression yielded the equation:

predicted SFR = 3.91 - 0.55 (PET defect rank)

with standard errors for the coefficients of 1.4 and 0.04, respectively. This regression equation is provided for description rather than for calculations; because of the scatter in the relation, direct calculation of any individual value of SFR from PET defect score would not be accurate. Mean values are shown for clarity because of overlap of the large number of data points; regression was performed with the raw data. Although the correlation coefficient is negative, the slope is positive in Figure 3, top, because the vertical scale was reversed in the figure for convenience so that SFR would parallel stenosis severity.

PET Defects Compared With Arteriographic Severity for Each Patient

To determine whether PET defects identify patients with coronary disease, irrespective of location, the SFR of the most severe stenosis was compared to the score of the most severe PET defect for each patient over the entire range of disease severity (Figure 3, bottom).

As in the preceding figure, increasing impairment of flow reserve corresponds to increasing PET defect severity. Although there is wide scatter, a PET defect score of 2 or more (indicated by the vertical line in Figure 3, bottom) is predictive of significant flow impairment (SFR < 3). The SEMs are larger for the middle range of stenosis severity (from 2 to 4) than for the extremes. This is attributable in part to the smaller numbers of PET defects in this range. In addition, several of these defects correspond to lesions in diagonal arteries or in distal portions of the larger arteries, affecting small regions of myocardium. The severity of such small defects

Figure 3. Top panel: Plot of the relation between arteriographic stenosis flow reserve and subjective PET defect severity in the corresponding anatomic region for 243 stenoses. Mean value of SFR is plotted as a function of PET defect severity. The horizontal dashed lines identify the ranges of normal, mildly reduced, and significantly reduced stenosis flow reserve. The vertical dashed line indicates that PET defect scores of 2 or more predict the presence of mild or significant stenoses. The error bars represent 90% confidence intervals. The number of patients represented is shown adjacent to each point. Right-hand column lists the numbers of patients found in each interval of SFR, to illustrate the distribution of coronary disease in this population. SFR is plotted on a reverse scale (5 to 0) to parallel stenosis severity. No error bars are shown for the point representing a single stenosis. Bottom panel: Plot of the relation between arteriographic stenosis flow reserve and subjective PET defect severity in 174 patients. The most severe stenosis was compared with the most severe PET defect for each patient. Nineteen patients with revascularization during acute infarction were excluded because the residual stenosis severity would not be comparable to the severity of the fixed perfusion defect. As for the top panel, the horizontal dashed lines identify the ranges of normal, mildly reduced, and significantly reduced stenosis flow reserve. The vertical dashed line indicates that PET defect scores of 2 or more predict the presence of mild or significant stenoses.
TABLE 2.  Interobserver Differences in PET Scores

<table>
<thead>
<tr>
<th>Agreement</th>
<th>Difference</th>
<th>Maximal score</th>
<th>Maximal score</th>
<th>Maximal score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rest scans</td>
<td>Stress scans</td>
<td></td>
</tr>
<tr>
<td>Identical</td>
<td>0</td>
<td>75 (40%)</td>
<td>59 (31%)</td>
<td></td>
</tr>
<tr>
<td>Essential</td>
<td>1</td>
<td>66 (35%)</td>
<td>86 (45%)</td>
<td></td>
</tr>
<tr>
<td>Near</td>
<td>2</td>
<td>14 (7%)</td>
<td>14 (7%)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>19 (10%)</td>
<td>16 (8%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>4</td>
<td>4 (2%)</td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>Marked</td>
<td>5</td>
<td>11 (6%)</td>
<td>11 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

Percent in parentheses.

Interobserver differences in subjective scoring of PET scans by two independent readers blinded to angiographic and clinical data. Results are tabulated according to the maximum difference in scores assigned to each region by the two readers. Only one reading was available for two patients.

may be blunted by the partial volume effect which is a function of camera resolution.

PET defect severity correlated significantly with arteriographic stenosis severity ($r = 0.77 \pm 0.06$). Linear regression yielded the equation:

predicted SFR = 4.14 - 0.70 (PET defect rank)

with standard errors for the coefficients of 0.14 and 0.04, respectively. As above, this equation is provided for description rather than for calculations. As for Figure 3, top, mean values are used for clarity; regression was performed with the raw data. The problem of false-positive scans is described below.

Special Cases and Exceptions

One patient with a long intramyocardial portion or “muscle bridge” of the proximal left anterior descending artery had a moderate PET defect of the anterolateral wall. Two patients had defects of the resting PET scan which normalized with stress; one of these two patients had an arterioatrial fistula; the other had no evidence of coronary disease.

Results of nine patients deviated significantly from the pattern. Two patients with minimal stenosis severity (SFR > 4) had PET defects with scores more than 2. One with a stress PET defect score of 4.5 reported smoking five cigarettes immediately before the imaging. A repeat scan performed after the patient quit smoking was normal. The other patient with a PET defect score of 3 had undergone recent transluminal coronary angioplasty with subsequent angiographic dissection of the artery supplying the region of the PET defect, suggesting early restenosis or closure.

Seven patients with significant CAD (SFR < 3) had PET scores less than 2 or no defect. None of these seven cases involved proximal disease; in five, SFR was greater than 2.5. Mild LAD and diagonal lesions were more often missed than mild disease of other arteries, possibly due to difficulty distinguishing normal apical thinning from mild perfusion defects.

PET Defect Location Compared With Site of Coronary Disease

PET defect location was compared to arteriographic localization for each patient. Results for patients with one-vessel disease are shown in Table 1. For patients with multivessel disease, 55 of 77 had multiple PET defects. In patients with mild or significant right and left circumflex coronary stenoses, five of 11 inferoposterior defects had associated lateral defects. In combined LAD-RCA disease, 11 of 13 patients had both anterior and posterolateral defects. Overall, anterior PET defects were associated with LAD or diagonal disease and posterior defects were associated with either left circumflex or right coronary disease.

Rest PET Defects Compared With Myocardial Infarction

Sixty-six patients had a clinical diagnosis of previous myocardial infarction. Fifty-one (77%) of these had resting PET defects and 18 of these had additional or more severe defects with stress. Fifteen patients with previous infarction had normal rest scans. Of these 15 exceptions, eight had undergone acute intervention with intravenous or intracoronary thrombolytic agents and/or transluminal balloon coronary angioplasty. Another five of the exceptions had non-Q wave infarctions only. The remaining two had well-developed collaterals.

Rest PET defect severity was less than two in 100 of 127 patients (79%) with no clinical diagnosis of myocardial infarction. Eight of the 27 exceptions had complete occlusions of at least one epicardial coronary artery. Three had regional wall motion abnormalities documented by gated nuclear or contrast ventriculography. Another eight had severe coronary stenoses, with SFR values less than two. There was no evidence of previous infarct in the remaining eight patients with abnormal rest scans; in two of these eight patients, scans normalized with stress, and the remaining six had abnormal stress scans as well.

Interobserver Differences in PET Scan Interpretation

In 82% of rest scans and 83% of stress scans, the two numeric scores were in agreement (Table 2). For 89% of patients, readers agreed on the overall interpretation of the presence (PET score > 2) or absence of defects (PET score < 2) in the rest/stress scans. Disagreement most often involved the apex and inferoposterior wall. Forty-eight of 75 rest scans with identical readings were normal, and 40 of 59 stress scans with identical readings were normal.

Comparison With Thallium Scintigraphy

This study did not specifically compare PET imaging to other, more widely available, methods such as
20\textsuperscript{TI} scintigraphy. Available data are not directly comparable because of the limitations of sensitivity/specificity analysis described in the introduction.

One recent study, by Zijlstra and colleagues,\textsuperscript{30} reported the sensitivity and specificity of exercise thallium compared with radiographic coronary flow reserve in 38 patients with one-vessel disease. It is not directly comparable because of major differences in methods, including binary classification, number and selection of patients, coronary flow reserve compared with stenosis flow reserve, and exercise compared with dipyridamole stress. However, this is the only previous study, to our knowledge, in which imaging data are compared with a continuous scale of flow reserve (FR), permitting indirect comparison to the present results. 1) For moderate to severe stenoses (FR<3), 72% (18 of 25) of thallium scans compared with 94% (108 of 115) of PET scans were negative. 2) For intermediate stenoses (FR=3–4), 0% (0 of 9) of thallium scans compared with 49% (18 of 37) of PET scans were positive. 3) For minimal stenoses (FR≥4), 100% (4 of 4) of thallium scans compared with 95% (39 of 41) of PET scans were negative. Three categories were compared because the small number of patients in the thallium study did not permit finer divisions, and correlation coefficients were not available for the thallium data. The intermediate range of 3–4 is used for simplicity, but it closely approximates the 95% confidence interval of stenosis flow reserve at the cut-off value of 3.4–3.5 established by other investigators.\textsuperscript{30,31} This comparison is limited because of the small number of thallium patients, especially in the range of normal and less severe disease; the specificity of thallium may be overestimated because of the small proportion of women, reducing the effect of attenuation artifacts.

\textbf{Comparison of 82\textsuperscript{Rb} with 13\textsuperscript{N} Ammonia}

Images obtained with 82\textsuperscript{Rb} and 13\textsuperscript{N} ammonia tracers were qualitatively similar. The two false positive cases included one 13\textsuperscript{N} ammonia and one 82\textsuperscript{Rb} image. Of the seven false negative scans, five were ammonia scans and two rubidium. Thus, 79 of 82 rubidium images and 105 of 111 ammonia images were consistent with the arteriographic results. These ratios were not significantly different (p=0.73).

\textbf{Discussion}

The accuracy of positron perfusion imaging of the heart has been reported in previous studies of the feasibility of clinical dipyridamole-PET imaging. Schelbert and colleagues\textsuperscript{16} compared PET scan results to percent diameter narrowing and found sensitivity and specificity values of 97% and 100%. According to standard statistical tables,\textsuperscript{32} the lower limits of the 95% confidence intervals for these values are 84% and 75%, respectively. In a study of 50 patients by Gould et al,\textsuperscript{17} PET scan results were compared with quantitative arteriographic stenosis flow reserve, and sensitivity and specificity were found to be 95% and 100%. The corresponding lower limits of the 95% confidence intervals are 77% and 66%. The lower limits of the 99% confidence intervals are 71% and 56%. The overlap of these wide confidence intervals with the sensitivity and specificity values reported for planar thallium imaging, and even electrocardiographic exercise testing, indicate the need for larger numbers of patients for statistical accuracy.

The present study differs from earlier reports of perfusion imaging accuracy in the combined use of quantitative arteriographic stenosis flow reserve rather than percent diameter narrowing as the gold standard, the large number of patients, and the use of correlation rather than binary sensitivity-specificity analysis.

\textbf{Stenosis Flow Reserve Compared With Coronary Flow Reserve}

It is important to distinguish stenosis flow reserve,\textsuperscript{33} which is calculated from static quantitative arteriographic dimensions, compared with coronary flow reserve, which is derived from direct measurement of the instantaneous ratio of hyperemic to rest flow. Coronary flow reserve depends on perfusion pressure, coronary venous pressure and/or arteriolar tone, and strength of the hyperemic stimulus; two stenoses of exactly the same geometry may have entirely different values of coronary flow reserve in different patients, or even in the same patient under different hemodynamic conditions. SFR, in contrast, is independent of hemodynamic conditions. It describes the conductance of the stenosis itself as if the arterial segment were excised and studied in vitro under controlled conditions. In the present application, this feature is advantageous because it allows comparison between patients. Neither measurement is superior; each
measures a different aspect of the stenosis, and each is applicable to a different clinical question.

**Stenosis Flow Reserve Compared With Diameter Narrowing**

The advantages of SFR over percent diameter narrowing, including the use of all relevant dimensions and absolute dimensions to allow for diffuse disease, have been described previously. To assess the importance of dimensions other than percent diameter narrowing that enter into the equation for stenosis flow reserve, calculated SFR was plotted as a function of percent diameter narrowing for the first 100 patients (Figure 4). Further patients were not included because of overlap of data points. The scatter in this relation represents the effect of factors other than relative diameter, such as length, absolute cross-sectional area, and expansion angle, that determine stenosis flow reserve. These data reveal important limitations of the use of percent diameter narrowing as the sole indicator of stenosis severity, even when it is measured accurately. For arteries with 50% diameter narrowing, stenosis flow reserve ranges from 2.8 to 4.5. The spread is even wider for 60% narrowing. Many stenoses with more than 50% diameter narrowing have only mild or minimal reduction in SFR. Of 107 stenoses with more than 50% diameter narrowing, 30% had only mild SFR reduction (SFR≥3), and 8% had nearly normal coronaries (SFR≥4). Thus, true-negative perfusion scans associated with such lesions would be labeled as false-negative, if 50% diameter reduction alone were used to define significant coronary disease. In some studies, the criterion for significant coronary stenoses is 75% diameter narrowing. This cut-off point, or even 70% diameter narrowing, classifies a large number of stenoses with a significantly reduced SFR as negative. One third of stenoses with less than 75% diameter narrowing had significantly reduced stenosis flow reserve (SFR<3), and 16% of these were severely narrowed (SFR<2). As a result, true-positive scans associated with such lesions would be labeled as false-positive, were 75% diameter narrowing alone used to define significant coronary disease.

**PET Defect Severity Compared With Stenosis Severity**

PET defect severity correlated significantly with arteriographic stenosis severity in both the regional and patient-by-patient analysis. However, there was considerable scatter in these relations which may be attributable to the subjective scoring of PET defects or other limitations described below.

**Rest PET Compared With Myocardial Infarction**

The relation between PET defects and myocardial infarction has been previously described in a smaller group of patients. The present results confirm that resting perfusion defects seen by PET correspond to clinical myocardial infarction.

**Interobserver Agreement**

Interobserver disagreement occurred primarily in scans of patients with mild coronary disease and those with small defects. The finding of 75% and 76% identical or essential agreement for rest and stress scans, respectively, is comparable with the 79% exact or essential interobserver agreement reported for TI images with a slightly different analytic method.

**Potential Limitations**

The use of a subjective scoring method for PET defect severity most likely accounts for much of the scatter in the relations in Figure 3. Quantitative methods for describing PET defect severity have been described, such as measurement of relative myocardial perfusion reserve. However, this technique was not practical for the large number of patients in the present study because it requires subjective border delineation for regional analysis and assumes the presence of a normal region of myocardium in each patient. Technical limitations of quantitative PET imaging include cardiac motion, patient motion, partial volume errors, and decreased extraction of perfusion tracers at high flows. Subendocardial infarction may add to apparent error by introducing a partial-thickness perfusion defect without a correspondingly severe stenosis in the supply artery.

Stenoses in series may not have been accurately assessed. Only the single most severe stenosis was used to represent each artery because stenoses in series do not necessarily behave as additive resistances, due to intervening branches, and criteria for quantitative analysis of such lesions have not been established.

Anatomic variations in the coronary tree and overlap of perfusion beds limited the accuracy of matching each stenosis to a corresponding defect. For this reason, an additional analysis was performed to compare results for individual patients irrespective of defect location. This effect would tend toward underestimation of the relation between PET defect and stenosis severity by contributing to scatter. In addition, variation in perfusion bed size may cause arteries with equally severe stenoses to have variable sizes of PET defect.

Stenosis flow reserve may not correspond to PET perfusion reserve in the presence of altered physiologic conditions such as very high or low perfusion pressure and heart rate, collateral flow, increased resting flow, ventricular hypertrophy, abnormal venous pressure, or inadequate vasodilatory stimulus. Although direct measurement of coronary flow reserve reflects these conditions, except for collateral flow, it may not be advantageous because hemodynamic conditions are likely to change between the times of catheterization and PET imaging.
Summary

Traditionally, noninvasive tests for the detection of coronary artery disease have been compared with percent diameter stenosis using binary classification and sensitivity-specificity analysis. Recent analyses have indicated the need for comparison to a more accurate gold standard and the use of continuous rather than binary outcome variables. In the present study, subjective PET defect severity and quantitative arteriographic stenosis flow reserve, a more physiologic gold standard, were compared over the full spectrum of coronary disease severity. Results indicate that subjective severity of regional PET perfusion defects correlates significantly with the calculated stenosis flow reserve of the corresponding coronary arteries.

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