Phase II Safety and Clinical Comparison With Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging for Detection of Coronary Artery Disease

Flurpiridaz F 18 Positron Emission Tomography

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Objectives
This was a phase II trial to assess flurpiridaz F 18 for safety and compare its diagnostic performance for positron emission tomography (PET) myocardial perfusion imaging (MPI) with Tc-99m single-photon emission computed tomography (SPECT) MPI with regard to image quality, interpretative certainty, defect magnitude, and detection of coronary artery disease (CAD) (≥50% stenosis) on invasive coronary angiography (ICA).

Background
In pre-clinical and phase I studies, flurpiridaz F 18 has shown characteristics of an essentially ideal MPI tracer.

Methods
One hundred forty-three patients from 21 centers underwent rest-stress PET and Tc-99m SPECT MPI. Eighty-six patients underwent ICA, and 39 had low-likelihood of CAD. Images were scored by 3 independent, blinded readers.

Results
A higher percentage of images were rated as excellent/good on PET versus SPECT on stress (99.2% vs. 88.5%, p < 0.01) and rest (96.9% vs. 66.4, p < 0.01) images. Diagnostic certainty of interpretation (percentage of cases with definitely abnormal/normal interpretation) was higher for PET versus SPECT (90.8% vs. 70.9%, p < 0.01). In 86 patients who underwent ICA, sensitivity of PET was higher than SPECT (78.8% vs. 61.5%, respectively, p = 0.02). Specificity was not significantly different (PET: 76.5% vs. SPECT: 73.5%). Receiver-operating characteristic curve area was 0.82 ± 0.05 for PET and 0.70 ± 0.06 for SPECT (p = 0.04). Normalcy rate was 89.7% with PET and 97.4% with SPECT (p = 0.008). Extensive safety assessment revealed that flurpiridaz F 18 was safe in this cohort.

Conclusions
In this phase 2 trial, PET MPI with flurpiridaz F 18 was safe and superior to SPECT MPI for image quality, interpretative certainty, and overall CAD diagnosis. (J Am Coll Cardiol 2013;61:469–77) © 2013 by the American College of Cardiology Foundation

Over the past 4 decades, radionuclide myocardial perfusion imaging (MPI) has become the mainstay of stress imaging for the evaluation of patients with suspected or known coronary artery disease (CAD). The method offers objective means of detecting stress-induced perfusion defects due to hemodynamically significant coronary stenoses, thereby providing an important tool in risk stratification and guiding patient management (1–3). Although the radiopharmaceuticals commonly used for MPI are distributed to the myocardium in proportion to myocardial perfusion, a limitation of widely available radiopharmaceuticals used for this purpose has been a “roll-off” of their uptake at higher levels.
of coronary flow (4–9). As a consequence, mild reductions in maximal achievable coronary flow might not result in corresponding decreases in myocardial tracer uptake. Furthermore, these agents have lower spatial resolution than the positron emission tomography (PET) agents fluorine-18 (F-18) and nitrogen-13. These limitations have long been the impetus toward the development of radiopharmaceuticals that would have superior uptake versus flow relationships at peak flow rates as well as higher image resolution. Short-lived cyclotron-produced PET MPI agents, including oxygen-15 water and nitrogen-13 ammonia, have excellent flow versus uptake characteristics at high flow rates (10,11); however, these tracers are not practical for widespread clinical use due to the requirement that they be used in very close proximity to medical cyclotrons.

Flurpiridaz F 18, labeled with positron-emitting isotope F-18, has recently been developed as an MPI radiopharmaceutical for use with PET (12–17). In pre-clinical as well as phase I studies, flurpiridaz F 18 has been shown to have essentially linear myocardial uptake throughout the range of flow (13,17). It also has high myocardial retention, low background in adjacent organs, and other characteristics that suggest it might be close to an ideal myocardial perfusion tracer (7,15,16). The purpose of this phase II trial was to assess the diagnostic efficacy for detection of CAD.

Methods

Study population. Patients were eligible for the study if they were referred for clinically indicated single-photon emission computed tomography (SPECT) MPI or if they had undergone invasive coronary angiography (ICA) without percutaneous coronary intervention (PCI) within 60 days. Patients were recruited from 21 centers in the United States. All potential child-bearing female patients underwent pregnancy testing within 24 h before receiving the PET tracer. Patients were not eligible for the study if they were <18 years of age, had PCI or coronary artery bypass grafting within 6 months before either PET or SPECT, had nonischemic cardiomyopathy or an ejection fraction of <35%, or were unable to undergo exercise or pharmacological stress testing. The study was approved by the institutional review boards of all participating centers, and all patients provided written informed consent.

Study design. All patients underwent SPECT MPI within 90 days before or 60 days after flurpiridaz F 18 PET MPI. If SPECT MPI had been performed before enrollment on an accepted SPECT camera, repeat SPECT examination was not performed. In those without such a SPECT study, both SPECT and PET scans were performed for purposes of the research trial during the study. In patients who had ICA, the ICA was performed within 60 days of PET MPI.

All patients were evaluated for flurpiridaz F 18 safety. Patients who underwent any imaging were evaluated for image quality and diagnostic certainty. Patients who underwent ICA were evaluated for test performance characteristics, whereas those who did not undergo ICA but who could be classified as low CAD likelihood were evaluated for normalcy rate.

Stress testing protocols. Stress tests were performed with either exercise or pharmacological stress according to American Society of Nuclear Cardiology Guidelines (18), with the intention to have the same stress test for both procedures. Exercise testing was performed with a standard Bruce exercise treadmill protocol, and the radiopharmaceutical was injected at the same time-point during the SPECT and PET procedures. Pharmacological stress tests were conducted with adenosine, regadenoson, or dipyridamole. Patients were instructed to have no caffeine intake for 24 h before pharmacological stress testing and were taking the same cardiac active medications at the time of both SPECT and PET studies.

SPECT imaging protocol. Tc-99m agents were used for all SPECT imaging (73 Tc-99m sestamibi and 35 Tc-99m tetrofosmin in 1-day protocol; 10 Tc-99m sestamibi and 6 Tc-99m tetrofosmin in 2-day protocol). There were 19 cases performed with the rest TI-201 and stress Tc-99m dual isotope MPI protocol. All PET and SPECT cameras used in the study were subjected to and passed quality control procedures reviewed by the core laboratory for purposes of the study. The SPECT scanning was performed with standard American Society of Nuclear Cardiology Guidelines with either rest/stress or a stress/rest protocol (18).

PET imaging protocol. All PET imaging was performed at rest and stress in accordance with the pre-defined study protocol with either PET/computed tomography (CT) systems (n = 140) or dedicated PET scanners (n = 3). All PET cameras used in the study were subjected to quality control procedures for the purpose of this study. For PET/CT, attenuation correction CT scans were obtained before rest and stress examinations. For dedicated PET, transmission scans for attenuation correction scans were performed with a radioisotope source. Imaging was performed in list-mode. Rest imaging began at the time of the flurpiridaz F 18 injection and was continuously acquired.
Rest, and 6.76

The native coronary arteries. Arteries with patent stents were

absence of CAD was strictly related to coronary stenosis in

absence of CAD. The determination of the presence or

infarction (MI). Presence or absence of wall motion abnor-

mality was not considered in interpreting the presence or

stenoses defined the presence of significant CAD. The core

when there was

imaging results. A coronary stenosis was considered present

(Perfuse, Boston, Massachusetts) blinded to the clinical or

angiography (QCA) in a coronary angiography core laboratory

Coronary angiography interpretation. Coronary angiograms were interpreted with quantitative coronary an-

supine SPECT images.

For patients who underwent attenuation-corrected

studies in independent cross-over reading sessions. The

readers were blinded to which study was being performed,

the type of stress, patient sex, and all clinical data as well as

to the reading of other readers. Image quality was classified

as excellent, good, fair, poor, or uninterpretable. Certainty

of overall interpretation was classified definitely normal,

probably normal, probably abnormal, and definitely

abnormal.

For the purpose of assessing diagnostic efficacy, each

blinded reader rated the rest/stress perfusion and gated

images as normal, ischemic, ischemic and scar, or scar. A

patient was considered MPI negative if the rating was

normal. Summed stress scores (SSS), summed rest scores

(SRS), and summed difference scores (SDS) were calcu-

lated by the core laboratory (18). A patient was consid-

ered to have a reversible defect when the SDS was ≥2.

For patients who underwent attenuation-corrected

SPECT or both supine and prone SPECT acquisitions,

the readers assessed only the non–attenuation-corrected,

supine SPECT images.

Coronary angiography interpretation. All coronary an-

giograms were interpreted with quantitative coronary an-

giography (QCA) in a coronary angiography core laboratory

(Perfuse, Boston, Massachusetts) blinded to the clinical or

imaging results. A coronary stenosis was considered present

when there was ≥50% diameter stenosis in any epicardial

coronary artery. The presence of 1 or more coronary stenoses defined the presence of significant CAD. The core

laboratory had no knowledge of history of myocardial

infarction (MI). Presence or absence of wall motion abnor-

mality was not considered in interpreting the presence or

absence of CAD. The determination of the presence or

absence of CAD was strictly related to coronary stenosis in

the native coronary arteries. Arteries with patent stents were

classified as no significant CAD, regardless of evidence of

prior MI. Arteries with patent bypass grafts but native

coronary stenosis were classified as significant CAD.

Safety analysis. Safety assessments included blood and

urine testing as well as clinical monitoring for possible

adverse events (AEs). Patients were monitored for 30 min

after the rest injection and for 60 min after the stress

injections for clinical symptoms, vital signs, and electrocar-
diogram changes. They were followed for 2 weeks after

the drug administration for AEs. All AEs were adjudicated by

the site principal investigator, including whether they were

considered to be related to the drug or to the stress test. A

serious AE was defined as any AE considered life threat-

ening, resulting in death, requiring in-patient hospital stay,

or persistent or significant disability/incapacity.

Statistical analysis. Continuous variables were expressed as mean (or median) and range or SDs. Paired continuous

variables that were not normally distributed were compared

with the Wilcoxon signed rank test for matched pairs or the

paired t test if normally distributed. Categorical variables

were expressed as frequencies. Primary diagnostic efficacy

measures were sensitivity and specificity and were assessed

after blinded and independent reads of PET MPI and

SPECT MPI data with ICA as the truth standard (n = 86).

Efficacy estimates for PET MPI and SPECT MPI were

compared individually with a 2-sided paired test of

proportions (McNemar test) at 5% level of significance.

Normalcy rate was determined in the patients with a low

likelihood of CAD and no ICA and was calculated as

percentage of patients with normal/probably normal

studies. Analysis of diagnostic efficacy was performed by

reader as well as with majority rule, and the results of

majority rule analysis were used in the overall efficacy

analysis. Where majority rule was used for the compari-

son between PET and SPECT MPI, the estimate was

obtained with the rating obtained by 2 of 3 blinded

readers for each patient. The analysis of diagnostic

certainty used a modified majority rule in which the

median rating was used when 3 readers have 3 different

ratings. Summaries and comparisons of SRS, SSS, and

SDS measures similarly used the median of the results of

3 blinded readers. Receiver–operating characteristic

(ROC) curve analysis was performed in the 86 patients

undergoing ICA with the comparison of area under ROC

between PET MPI and SPECT MPI diagnostic efficacy.

The area under ROC and confidence intervals used the

empirical approach developed by DeLong et al. (19).

The interreader agreement between 3 blinded readers was

estimated by comparison of dichotomized ratings (normal/

abnormal) and was presented with kappa and percentage

agreement. Intradate agreement for each of the readers

was performed by randomizing 10% of the repeat images in

the blinded read and was estimated with kappa and per-

centage agreement.
Results

Patient population characteristics. There were 143 patients enrolled into the overall study population, 107 men, and the mean age was 62.5 years (Table 1). The mean body mass index was 28.3. There were 108 white, 3 Asian, 16 African American individuals, and 16 who classified themselves as “other” race/ethnicity. Patients were stratified into 3 pre-test CAD likelihood categories: low (n = 45); intermediate (n = 68); and high (n = 30) (18,20), the latter including patients with known CAD. In the angiographic cohort (n = 86), 52 patients had significant CAD by QCA, and 34 patients had no significant CAD or normal coronary arteriograms. In this cohort, 70 patients had SPECT studies performed before PET and ICA; 15 patients had ICA before PET and SPECT studies, and 1 patient had PET study completed before ICA and SPECT study. In this cohort, 22 had prior MI, 42 had prior revascularizations, and 43 had either prior MI or revascularization. Figure 1 depicts the manner in which the 143 patients were enrolled and evaluated. Eleven patients were excluded for the reasons listed, leaving 132 patients who had both SPECT MPI and PET MPI studies evaluable for image quality and diagnostic certainty comparison. Seven patients of the 132 with an intermediate or high likelihood of CAD did not undergo ICA. The remaining 125 patients were evaluable for diagnostic efficacy and included 86 with ICA evaluated for sensitivity and specificity for angiographic CAD and 39 patients with a low likelihood of CAD assessed for normalcy rate.

Stress flurpiridaz F 18 PET MPI was performed with either exercise (n = 76) or adenosine (n = 67) stress. For SPECT MPI, pharmacological stress was conducted with adenosine (n = 44), regadenoson (n = 7), or dipyridamole (n = 10). A total of 5 of 143 patients had different stress test types between 2 MPI procedures.

Clinical safety. Among the 132 patients in the safety population, 2 patients reported a total of 3 serious AEs (dizziness, hypertension, and knee effusion) that were judged to be unrelated to study drug. Sixty-one patients (42.7% of the 143) reported 108 AEs. Thirty-six of these 61 patients received pharmacological stress with a total of 75 AEs, and the remaining 25 patients received exercise stress with a total of 33 AEs. One hundred of the 108 AEs were considered not related to study drug. Of the remaining 8 AEs judged as possibly or probably related to the study drug, all were of either mild or moderate severity and resolved without any complications. Five of these 8 were also judged as possibly or probably related to the stress test itself. The remaining 3 of the 8 patients had the following: transient hypertension, mild cough, and a metallic taste. The AEs associated with the Tc-99m and Tl-201 injections were not obtained. There was no evidence of clinically relevant flurpiridaz F 18 effect on QT interval in this study. An independent data-monitoring committee that reviewed safety data at regular intervals did not raise any significant safety concerns.

Image quality. Among the 132 patients assessed for image quality, image quality was judged to be superior with flurpiridaz F 18 for both stress and rest (Fig. 2). On the stress studies, 99.2% were considered to be good or excellent with flurpiridaz F 18 versus 88.5% with Tc-99m (p < 0.01). On the rest studies, image quality was considered to be good or excellent in 96.9% with flurpiridaz F 18 versus 66.4% with Tc-99m (p < 0.01). Excellent image quality alone was observed on stress images in 80.9% with flurpiridaz F 18 and in 24.4% with Tc-99m (p < 0.01) and on rest studies in 69.5% with flurpiridaz F 18 versus 7.6% with Tc-99m (p < 0.01).

Diagnostic certainty. In the overall efficacy population of 132 patients, diagnostic certainty was greater with flurpiridaz F 18 than with Tc-99m (Fig. 3). Certainty of interpretation was classified as definitely normal or definitely abnormal in 90.8% of patients by flurpiridaz F 18 and in 70.9% of patients by Tc-99m (p < 0.01), with approximately a 3-fold reduction in the patients in the probably normal and probably abnormal groups.

Detection of CAD. In the 86 patients who underwent ICA and thus had a truth standard for coronary stenosis, 52 had significant CAD on ICA. The sensitivity of PET was higher than that of SPECT (78.8% vs. 61.5%, respectively, p = 0.02). The specificity was not significantly different (76.5% for PET vs. 73.5% for SPECT) (Fig. 4). The area under the ROC curve was 0.82 ± 0.05 for PET and 0.70 ±

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient Characteristics</th>
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<tbody>
<tr>
<td></td>
<td>Efficacy Population (n = 125)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>62.3 (29-85)</td>
</tr>
<tr>
<td>Age ≥65 yrs</td>
<td>59 (47.2)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>97 (77.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>African American</td>
<td>13 (10.4)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (9.6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>92 (73.6)</td>
</tr>
<tr>
<td>Female</td>
<td>33 (26.4)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.6 (18-42)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>22 (17.6)</td>
</tr>
<tr>
<td>CABG</td>
<td>14 (11.2)</td>
</tr>
<tr>
<td>PCI</td>
<td>28 (22.4)</td>
</tr>
<tr>
<td>CABG or PCI</td>
<td>42 (33.6)</td>
</tr>
<tr>
<td>Prior MI or revascularization</td>
<td>43 (34.4)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>56 (44.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>29 (23.2)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>53 (42.4)</td>
</tr>
<tr>
<td>Pre-test likelihood of CAD</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>41 (32.8)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>58 (46.4)</td>
</tr>
<tr>
<td>High</td>
<td>26 (20.8)</td>
</tr>
</tbody>
</table>

Values are mean (min–max) or n (%).

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.
0.06 for SPECT (p = 0.04) (Fig. 5). In the 39 patients with a low likelihood of CAD, the normalcy rate was 89.7% with PET and 97.4% with SPECT (p = NS).

**Magnitude of stress and rest perfusion defect.** The SSS and SRS scores in the patients who underwent ICA are shown in Table 2 according to the number of vessels abnormal on ICA. In patients with 1- and 2-vessel stenosis, the median SSS was greater with PET than with SPECT.

**Magnitude and frequency of reversible perfusion defect.** The magnitude of reversible perfusion defect on PET and SPECT in the patients who underwent ICA is shown in Tables 3 and 4. In the patients with coronary stenosis (Table 3), the mean SDS and the proportion of patients with SDS ≥ 2 was higher with PET than SPECT as interpreted by each reader. In the patients without coronary stenosis (Table 4), the mean SDS and the proportion of patients with SDS ≥ 2 was not significantly different between the 2 MPI modalities for any of the readers.

**Reader agreement.** Interreader agreement rates for presence of abnormality were ≥90% in PET MPI between 3 readers with kappa values of ≥0.80 between readers. Intrareader agreement rates were slightly lower for SPECT MPI (≥80%) and kappa values of at least 0.60. Intrareader agreement rates for presence of abnormality were ≥90% in PET MPI between 3 readers with kappa values of ≥0.80 between readers. Intrareader agreement rates were slightly lower for SPECT MPI (≥80%) and kappa values of at least 0.60. Intrareader agreement rates for presence of abnormality were ≥90% in PET MPI between 3 readers with kappa values of ≥0.80 between readers. Intrareader agreement rates were slightly lower for SPECT MPI (≥80%) and kappa values of at least 0.60. Intrareader agreement rates for presence of abnormality were ≥90% in PET MPI between 3 readers with kappa values of ≥0.80 between readers. Intrareader agreement rates were slightly lower for SPECT MPI (≥80%) and kappa values of at least 0.60.
agreement rates were 80% or greater for both imaging modalities. **Case examples.** Examples of PET and SPECT images from a patient with no coronary stenosis on ICA are shown in Figure 6 and from a patient with left anterior descending coronary artery stenosis in Figure 7.

**Discussion**

This is the first multicenter clinical trial comparing the diagnostic performance of flurpiridaz F 18, a new myocardial perfusion PET tracer with conventional Tc-99m SPECT. Interpreted with rigorous core laboratory image analysis, the findings show that flurpiridaz F 18 can detect hemodynamically significant obstructive CAD with greater sensitivity, superior image quality, and with greater diagnostic certainty compared with SPECT MPI. The radiation doses associated with the flurpiridaz F 18 injections were approximately 2X lower than those associated with standard rest/stress Tc-99m SPECT MPI protocols. Importantly, in patients with significant coronary stenosis, the frequency and magnitude of reversible perfusion defect was greater with PET than SPECT. The extensive safety assessment conducted in this phase II study revealed that flurpiridaz F 18 was safe and well-tolerated in this study.

**Image quality and diagnostic certainty.** Variation of image quality and image interpretation has been considered one of the limitations of conventional SPECT MPI. In this study, image quality and diagnostic certainty were both higher with flurpiridaz F 18 PET than with SPECT. Image quality was good-to-excellent in a greater proportion of PET than SPECT scans and excellent in a far greater proportion of patients, both at stress and at rest. This superior image quality was associated with a higher diagnostic certainty with flurpiridaz F 18 by independent readers. The improved image quality and diagnostic certainty are likely due to the greater conspicuity of perfusion defects, improved resolution associated with F-18 PET, as well as the improved diagnostic certainty associated with the use of PET compared with SPECT and the use of attenuation correction for the PET studies (21). Of note, interreader agreement rates were high with both PET and SPECT and were higher with the PET examinations.

**Sensitivity and specificity for detection of CAD and magnitude of perfusion defects.** In this study we show that flurpiridaz F 18 PET was associated with improved sensitivity when compared with SPECT, with specificity similar to SPECT. Improved diagnostic accuracy was confirmed by a significantly greater receiver operating characteristics curve area for flurpiridaz F 18 PET compared with SPECT. Several factors might explain this improved sensi-

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**Table 2**

<table>
<thead>
<tr>
<th>Vessels Involved (n)</th>
<th>SSS PET</th>
<th>SSS SPECT</th>
<th>p Value</th>
<th>SRS PET</th>
<th>SRS SPECT</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (n = 34)</td>
<td>2.3</td>
<td>3.6</td>
<td>NS</td>
<td>1.0</td>
<td>1.5</td>
<td>NS</td>
</tr>
<tr>
<td>1 (n = 16)</td>
<td>9.7</td>
<td>6.5</td>
<td>&lt;0.05</td>
<td>3.0</td>
<td>2.8</td>
<td>NS</td>
</tr>
<tr>
<td>2 (n = 19)</td>
<td>10.5</td>
<td>5.1</td>
<td>&lt;0.05</td>
<td>1.3</td>
<td>2.2</td>
<td>NS</td>
</tr>
<tr>
<td>3 (n = 17)</td>
<td>13.1</td>
<td>14.3</td>
<td>NS</td>
<td>2.6</td>
<td>3.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

PET = positron emission tomography; SPECT = single-photon emission computed tomography; SRS = summed rest score; SSS = summed stress score.

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**Table 3**

<table>
<thead>
<tr>
<th>Reader</th>
<th>Statistic</th>
<th>PET</th>
<th>SPECT</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mean ± SD</td>
<td>8.9 ± 7.98</td>
<td>4.8 ± 5.61</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
<td>SD ≥2, n (%)</td>
<td>37 (71.2)</td>
<td>28 (53.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>3</td>
<td>Mean ± SD</td>
<td>9.4 ± 7.51</td>
<td>5.7 ± 6.51</td>
<td>0.01</td>
</tr>
<tr>
<td>4</td>
<td>SD ≥2, n (%)</td>
<td>36 (69.2)</td>
<td>26 (50.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>5</td>
<td>Mean ± SD</td>
<td>6.8 ± 5.75</td>
<td>4.1 ± 4.75</td>
<td>0.02</td>
</tr>
<tr>
<td>6</td>
<td>SD ≥2, n (%)</td>
<td>37 (71.2)</td>
<td>26 (50)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

N = 52.

PET = positron emission tomography; SPECT = single-photon emission computed tomography; SDS = summed different score.
tivity for CAD detection, including the higher extraction fraction of the tracer, the improved spatial resolution of PET versus SPECT, and the use of attenuation correction in the PET studies.

**Magnitude of perfusion defects.** The magnitude of stress and reversible perfusion defect with flurpiridaz F 18 PET was nearly double that of the Tc-99m SPECT studies in patients with coronary stenosis. The increased magnitude of perfusion defects in patients with angiographic stenosis was seen with each of the individual readers, as was the proportion of patients with disease-manifesting significant amounts of ischemia (SDS ≥ 2). The magnitude of perfusion defect was not different between the tracers in the patients without significant stenosis.

**Potential explanations for greater stress perfusion defect magnitude and higher sensitivity for CAD detection.** Flurpiridaz F 18 exhibits near-linear myocardial extraction and retention across the range of achievable myocardial blood flow (17). In contrast, a “roll off” of extraction at high myocardial perfusion rates has been reported for the commonly used SPECT agents Tc-99m-sestamibi, Tc-99m-tetrofosmin, and Tl-201 (4–7) as well as for the generator-produced PET agent Rb-82 (8,9). The higher extraction fraction of flurpiridaz F 18 compared with the SPECT tracers (17) at high flow rates is likely to be an important factor explaining the differences in magnitude of perfusion defect as well as higher sensitivity for perfusion defect detection observed in this study. During maximal exercise or with maximal coronary vasodilation, areas of the myocardium supplied by vessels without stenosis demonstrate myocardial perfusion rates in the range of 3 to 4 ml/min/g (8,22). These are perfusion rates at which a marked difference in uptake between tracers with high extraction fraction and low extraction fraction has been observed (4,5,17). By contrast, areas of the myocardium supplied by vessels with high-grade coronary stenosis have lower levels of maximal myocardial perfusion, which would manifest similar uptake between tracers with high- and low-extraction fractions (4). These factors would result in a greater magnitude of a stress perfusion defect with the more highly extracted agent. In regions supplied by a vessel with mild coronary stenosis, maximal myocardial perfusion would be expected to be only slightly reduced compared with those supplied by vessels without stenosis. This mild reduction in myocardial perfusion might be detectable with the more highly extracted tracer but might be insufficient to be detected by radiophar-

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**Table 4** Summary of SDS in Patients With Angiography-Negative Results

<table>
<thead>
<tr>
<th>Reader</th>
<th>Statistic</th>
<th>PET</th>
<th>SPECT</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mean ± SD</td>
<td>2.4 ± 5.26</td>
<td>3.1 ± 5.50</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>SDS ≥ 2, n (%)</td>
<td>8 (23.5)</td>
<td>14 (41.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>2</td>
<td>Mean ± SD</td>
<td>1.2 ± 3.57</td>
<td>2.7 ± 5.34</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>SDS ≥ 2, n (%)</td>
<td>4 (11.8)</td>
<td>9 (26.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>3</td>
<td>Mean ± SD</td>
<td>1.4 ± 2.85</td>
<td>1.6 ± 3.97</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>SDS ≥ 2, n (%)</td>
<td>8 (23.5)</td>
<td>6 (17.6)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

N = 34. Abbreviations as in Table 3.
maceuticals with lower extraction fraction (7), potentially contributing to the higher sensitivity observed with flurpiridaz F 18 than with the Tc-99m SPECT agents in this study. Improved spatial resolution of PET compared with SPECT and the use of attenuation correction with the PET studies might have contributed to the higher accuracy of flurpiridaz F 18 PET studies. In patients who had attenuation-corrected SPECT or both supine and prone SPECT imaging, only the supine SPECT imaging was assessed. Of note, the greater magnitude of reversible perfusion defect noted with flurpiridaz F 18 PET raises the possibility that reassessment of the threshold for ischemia used clinically to consider a study as indicating potential benefit from revascularization might have to be recalibrated in future studies.

Study limitations. This study has several limitations. Not all patients underwent ICA. The overall sensitivity of SPECT MPI in this study was generally lower than that reported in published clinical reports. These results are consistent with recent well-controlled SPECT MPI studies that implemented independent blinded read with multiple readers and have been conducted for regulatory purposes (23,24). Several factors might have led to this low sensitivity in both imaging modalities. Patient selection is likely to have been a significant contributor. Because the majority of the patients underwent both SPECT and PET before ICA, it is possible that patients with greater amounts of ischemia by SPECT or with greater symptoms might have been more likely to have been not referred for this trial, due to the desire of the clinician or the patient not to have an additional stress test before ICA. Because patients with recent ICA but no coronary intervention were not excluded from the trial, patients undergoing the PET examinations after ICA are more likely to have had angiographic lesions of only borderline significance at ICA, thus potentially reducing the sensitivity of both SPECT and PET. Additionally, in individuals with prior MI, the use of 50% stenosis QCA criteria might have led to a misclassification of patients, because fixed perfusion defects in these patients would be expected even if the infarct-related artery had been successfully opened at a prior PCI (i.e., if vessels in patients with prior PCI did not show ≥50% stenosis, the patients were categorized as normal, even if the vessels were supplying a region of MI). In this regard, 48 patients had undergone prior revascularization ≥6 months before the MPI studies, and 26 had prior MI. The determination of the presence or absence of CAD was based on coronary stenosis in the native coronary arteries; arteries with patent bypass grafts but native coronary stenosis were classified as significant CAD. The acceptance of patients into this trial who completed SPECT before ICA and had the PET study after ICA might have biased the population toward lower specificity by SPECT. The use of the >50% stenosis by ICA as the criterion for abnormality might have included patients as abnormal for the truth standard who do not have flow-limiting stenosis, falsely lowering the sensitivity of stenosis detection. The absence of flow-limiting stenosis in a substantial proportion of patients with >50% stenosis has been documented in studies comparing angiographic stenosis with abnormalities of coronary flow reserve as measured invasively by fractional flow reserve (24). Higher spatial resolution associated with PET compared with SPECT imaging methods might have contributed to the results. Attenuation correction was applied in the PET studies and not in the SPECT studies. Although this is the largest group of patients to be studied with this novel perfusion agent, the number of patients is still relatively small, and this might affect the statistical significance of our results.

Conclusions

Flurpiridaz F 18 PET, when compared with Tc-99m SPECT, has better image quality and shows higher diagnostic certainty. In patients with coronary stenosis by ICA, flurpiridaz F 18 PET manifests higher sensitivity than SPECT for detection of patients with coronary stenosis as well as greater magnitude of ischemia. These findings suggest that this new tracer might significantly improve the assessment of patients with radionuclide MPI compared with the standard SPECT MPI methods.

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