Evaluation of the Novel Myocardial Perfusion Positron-Emission Tomography Tracer $^{18}$F-BMS-747158-02 Comparison to $^{13}$N-Ammonia and Validation With Microspheres in a Pig Model

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**Background**—Positron-emission tomography (PET) tracers for myocardial perfusion are commonly labeled with short-lived isotopes that limit their widespread clinical use. $^{18}$F-BMS-747158-02 ($^{18}$F-BMS) is a novel pyridaben derivative that was evaluated for assessment of myocardial perfusion by comparison with $^{13}$N-ammonia ($^{13}$NH$_3$) and with radioactive microspheres in a pig model.

**Methods and Results**—Fourteen pigs injected with 500 MBq of $^{13}$NH$_3$ or 100 to 200 MBq of $^{18}$F-BMS underwent dynamic PET at rest and during pharmacological stress. In 8 of these pigs, $^{18}$F-BMS was injected during stress combined with transient, 2.5-minute constriction of the left anterior descending coronary artery. Radioactive microspheres were coinjected with $^{18}$F-BMS. Ratios of myocardial tracer uptake to surrounding tissues were determined, and myocardial blood flow was quantified by compartmental modeling. Both tracers showed high and homogeneous myocardial uptake. Compared with $^{13}$NH$_3$, $^{18}$F-BMS showed higher activity ratios between myocardium and blood (rest 2.5 versus 4.1; stress 2.1 versus 5.8), liver (rest 1.2 versus 1.8; stress 0.7 versus 2.0), and lungs (rest 2.5 versus 4.2; stress 2.9 versus 6.4). Regional myocardial blood flow assessed with $^{18}$F-BMS PET showed good correlation ($r=0.88$, slope=0.84) and agreement (mean difference $-0.10$ [25th percentile $-0.3$, 75th percentile $0.1$ mL · min$^{-1}$ · g$^{-1}$]) with that measured with radioactive microspheres over a flow range from 0.1 to 3.0 mL · min$^{-1}$ · g$^{-1}$. The extent of defects induced by left anterior descending coronary artery constriction measured by $^{18}$F-BMS and microspheres also correlated closely ($r=0.63$, slope=1.1).

**Conclusions**—$^{18}$F-BMS-747158-02 is a very attractive new PET perfusion tracer that allows quantitative assessment of regional myocardial perfusion over a wide flow range. The long half-life of $^{18}$F renders this tracer useful for clinical PET/CT applications in the workup of patients with suspected or proven coronary artery disease. (Circulation. 2009; 119:2333-2342.)

**Key Words:** positron-emission tomography ■ perfusion ■ ischemia ■ regional blood flow ■ microspheres

A unique feature of positron-emission tomography (PET) is that myocardial blood flow (MBF) and coronary flow reserve can be quantified in absolute terms over a wide flow range. Owing to high temporal resolution and accurate correction of photon attenuation, PET provides accurate delineation of regional tracer kinetics, which are used in combination with validated tracer kinetic models to quantify MBF in terms of mL · min$^{-1}$ · g$^{-1}$ of tissue.$^1$ These parameters have the potential to improve the accuracy of detecting coronary artery disease, particularly in patients with advanced disease.$^2$ They also allow detection and monitoring of changes in coronary microvascular reactivity with documented prognostic value in cardiomyopathies and patients at risk of coronary artery disease.$^3$–$^5$

**Editorial see p 2299 Clinical Perspective on p 2342**

Because of the distinct advantage that an on-site cyclotron is not required, the most commonly used radiopharmaceutical in myocardial perfusion PET is rubidium ($^{82}$Rb); however, the high kinetic energy of the emitted positrons results in an inferior spatial resolution compared with other PET isotopes.
13N-ammonia (13NH3) and 15O water are established perfusion tracers but require an on-site cyclotron. Because of their longer half-life, 18F-labeled tracers would avoid this limitation and facilitate clinical protocols. Such an agent, 18F-BMS-747158-02 (2-tert-butyl-4-chloro-5-[4-(2-(18F)fluoroethoxymethyl)-benzylxoy]-2H-pyridazin-3-1, or 18F-BMS [Figure 1]), was recently introduced for the evaluation of myocardial perfusion with PET.7 It is an analogue of the insecticide pyridaben that binds to the mitochondrial complex I of the electron transport chain with high affinity.8 Thus, this tracer shows selective uptake to the heart due to the high density of mitochondria in the myocardium. Initial experimental studies applying 18F-BMS in rat models have demonstrated excellent image quality and contrast between the heart and surrounding organs.9 Furthermore, extraction of 18F-BMS in the isolated perfused rat heart is high at different flow rates, which indicates suitability for quantification of MBF.9 However, owing to differences in mitochondrial density, cardiac physiology, and imaging hardware (preclinical versus clinical),10 these attractive properties of 18F-BMS remain to be verified in other species and large-animal models that more closely resemble the human heart. Moreover, suitability of 18F-BMS for quantification of MBF with a tracer kinetic model remains to be confirmed. Thus, we evaluated 18F-BMS for assessment of regional myocardial perfusion at rest and during pharmacological stress in a pig model. The quality of 18F-BMS PET images was evaluated in comparison to 13NH3, and absolute MBF values obtained with 18F-BMS and tracer kinetic modeling were validated with radioactive microspheres as the “gold standard.”

**Methods**

**Study Protocol**

The imaging protocols are shown in Figure 2. To evaluate 18F-BMS in the normal heart, 6 domestic pigs underwent dynamic PET after injection of 13NH3 at rest, followed by pharmacological stress (500 MBq for rest and 500 MBq for stress for NH3, and 100 MBq for rest and 200 MBq for stress for 18F-BMS). Perfusion was increased with variable doses of adenosine (150 to 500 μg · min⁻¹ · kg⁻¹ body weight) combined with dobutamine (10 to 40 μg · min⁻¹ · kg⁻¹ body weight) to maintain blood pressure. Variable doses of stressors were used to induce variation in hyperemic flow values. Infusion started 3 minutes before tracer injection and was maintained for 6 minutes. In 8 additional pigs, PET was performed after the left anterior descending coronary artery (LAD) was transiently constricted for 2.5 minutes during pharmacological stress, and 200 MBq of 18F-BMS was injected 30 seconds after the start of constriction.

The quality of 13NH3 and 18F-BMS PET images and activity ratios of cardiac to surrounding tissues were compared. To validate quantification of MBF, microspheres labeled with radioactive isotopes were injected simultaneously with 18F-BMS in all 14 animals. The microsphere-derived myocardial perfusion was compared with the results from tracer kinetic modeling of dynamic PET data. The
protocols were approved by the Commission of Animal Protection (Regierung von Oberbayern, Germany).

Animal Preparation and Surgery
The study was performed in young, healthy pigs (average weight 30 kg). After sedation with azaperone 2 mg/kg, ketamine 10 to 15 mg/kg, and atropine 0.5 to 1 mg/kg, the animals were given propofol 1% as an intravenous bolus. The animals were monitored continuously and ventilated with an oxygen/room air mixture of 60%/40%. Anesthesia was maintained with a continuous infusion of pentobarbital. Before interventions and from then on, fentanyl and atracurium were given every 30 minutes for analgesia and relaxation. Vascular access was prepared in the left and right vena jugularis externa and interna for drug infusions, in the left carotid artery for blood pressure measurement, and in the left femoral artery for blood withdrawal. Thoracotomy in the left fifth intercostal space was performed to insert a catheter into the left atrium for injection of microspheres and to gain access to the LAD. To create a region of reduced blood flow, a suture loop was constricted around the LAD immediately after the first diagonal branch until regional myocardial contraction abnormality was seen. The constriction was released after 2.5 minutes. After imaging, the animals were euthanized.

Tracer Production
The radiosynthesis and quality control of $^{18}$F-BMS have been described elsewhere.

Microsphere Measurements and Tissue Counting
Regional absolute myocardial perfusion at rest and after adenosine stress was measured with radioactively labeled microspheres ($^{194}$Ru and $^{95}$Nb, diameter 15 μm; Perkin-Elmer, Boston, Mass), which were always coinjected with $^{18}$F-BMS into the left atrium. Arterial reference blood samples were withdrawn with a calibrated pump starting 10 seconds before microsphere injection. After imaging, the animals were euthanized. Thoracotomy in the left fifth intercostal space was performed to insert a catheter into the left atrium for injection of microspheres and to gain access to the LAD. To create a region of reduced blood flow, a suture loop was constricted around the LAD immediately after the first diagonal branch until regional myocardial contraction abnormality was seen. The constriction was released after 2.5 minutes. After imaging, the animals were euthanized.

Data Analysis

Image Quality
Visual image quality was assessed by 2 observers blinded to the radiopharmaceutical on a 3-step score (poor, good, or excellent). For quantitative assessment, myocardial tracer activity ratios between the myocardium (lateral wall) and the lung, liver, and LV blood pool were calculated. Regions of interest were drawn in the last frame of the dynamic study and copied to all other frames to generate time-activity curves. To characterize residual activity in the blood, ratios of peak blood activity to activity at 5 and 10 minutes postinjection were calculated.

Image Quantification: Uptake, Myocardial Perfusion, and Defect Size
After the long axis of the LV was defined in transaxial slices, volumetric sampling was used to generate polar maps. These maps included the complete LV myocardium divided into 460 elements that represented myocardial count rates at each location at rest and stress, as described previously.13 Because of the long half-life of $^{18}$F, regional residual uptake from the first injection was determined in the first frame of the second study (acquired immediately before the second injection) and was subtracted from all later time points (Figure 3).

To study potential redistribution or washout of $^{18}$F-BMS, changes in myocardial uptake between 10 and 40 minutes postinjection were measured in normal and ischemic regions. For measurement of arterial input function, a cylindrical volume of interest (approximately $1.5\times1.5\times3$ cm$^3$) was automatically centered in the basal portion of the LV. No correction for metabolites was used. For every polar map element, 10- and 20-minute time-activity curves were generated from the dynamic study.

For measurement of $^{18}$F-BMS-derived MBF, a 3-compartment tracer kinetic model was used (Figure 1) based on the in vitro characteristics of the tracer: Lipophilicity (log $P$ value 2.73$^{14}$), fast uptake into cardiomyocytes ($T_{1/2}$ of 35 seconds in monolayers of neonatal rat myocytes$^{7}$), and very high cardiac first-pass extraction at different flow values (extraction of 0.94 in an isolated rat heart model$^{8}$). Because the single-pass extraction fraction was high, no corrections for a flow-dependent extraction were used. Because the dynamic images show very high retention, $k_c$ (the term that describes the back flux from the “trapped” compartment to the vascular space) was set to zero. The true myocardial activity is reduced by cardiac and respiratory motion and by the finite spatial resolution of PET, which results in partial volume effects. Furthermore, activity is increased by count spillover from the blood into the myocardium. To

Image Acquisition and Reconstruction
Imaging was performed with an ECAT HR+ PET tomograph (Siemens Medical Healthcare, Erlangen, Germany). After transmission imaging with rod sources, emission data were acquired in 2D mode. $^{11}$NH$\gamma$ dynamic series (12×10 seconds, 6×30 seconds, 3×5 minutes: 20 minutes) and the $^{18}$F-BMS dynamic series (12×10 seconds, 6×30 seconds, 7×5 minutes: 40 minutes) were acquired starting 10 seconds before tracer injection (slow 30-second bolus). Nongated, attenuation-corrected images were reconstructed with filtered back-projection (Hanning; cutoff frequency 0.3 cycle/bin, zoom 2.2, voxel size 2.34×2.34×3.38 mm$^3$, 63 slices).

Figure 3. Blood and tissue activity curves from sequential studies demonstrating the back flux subtraction and kinetic modeling (circles represent measured tissue data; diamonds, background corrected data; thin line, blood; thick line, model fit). Data from the first 5 minutes are shown as insets. a.u. indicates arbitrary units.
Correct for these effects, a modified volume-of-interests approach was used. The volumes of interest were constructed large enough that approximately 50% blood was included. Thus, the variable contributions to the myocardial signal were added to the model. To test whether the kinetic model could be further simplified, it was reduced to a 2-compartment model, ignoring the retention component, by using the initial 120 seconds.

Each of the 460 time-activity curves was submitted to a nonconstrained, nonlinear fitting routine (Marquardt-Levenberg). For MBF comparison between 13NH3 and the microspheres, a region in the polar map located at the center of the ischemic area and a region in the remote myocardium were selected. A previously validated 3-compartment model that included corrections for partial volume and spillover was used to analyze 13NH3. The defect size was expressed as a percentage of the LV below 50% maximum value by use of the MBF and the interpolated microsphere polar maps.

Statistical Analysis
Continuous variables are presented as median and interquartile ranges according to the syntax median (25th percentile; 75th percentile). Wilcoxon signed-rank test was used to assess differences in related measurements. Comparison between 2 independent samples was performed by Mann-Whitney U test. The Spearman correlation coefficient was used to evaluate bivariate relationships. A generalized estimating equation approach that assumed an exchangeable correlation structure in a linear regression model framework was used to assess accuracy of MBF estimates. The generalized estimating equation reflects the structure of repeated data and takes the correlation of measurements within the same animal into consideration. Significance of differences in slopes was evaluated by an interaction model term within the regression equation. Scatterplots and Bland-Altman plots were used, and in the latter, the estimated percentiles of differences (mean difference /H11006 1.96 SD) were calculated by the generalized estimating equation. Two-sided \( P \) values \( \leq 0.05 \) were considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Interventions and Hemodynamics
Surgical preparation of animals took an average of 1.5 hours. The results of the hemodynamic measurements at baseline and during stress are summarized in Table 1. Hemodynamics in rest and stress were comparable for both 13NH3 and 18F-BMS.

Image Quality in the Normal Myocardium
Typical 13NH3 and 18F-BMS images are shown in Figure 4. Blinded observers ranked the quality of 13NH3 images consistently as “good,” whereas 18F-BMS images were scored consistently as “excellent.”

Representative time-activity curves of 18F-BMS uptake in normal myocardium are given in Figure 3. They show a rapid vascular clearance approximately 3 minutes long followed by a stable tracer uptake.

Contrast ratios between normal myocardium and blood, liver, and lung 10 minutes after injection of tracers are summarized in Table 2. Figure 5 shows their changes over time. Myocardium-to-blood and myocardium-to-liver ratios approached a plateau phase after 10 minutes, whereas myocardium-to-lung ratio continued to increase. Contrast ratios of 18F-BMS were significantly higher than those of 13NH3.

Residual 18F-BMS blood activity remained stable, being 13% (10%; 16%) and 12% (10%; 14%) of the peak blood activity 5 and 10 minutes after injection at stress, respectively. The activity was comparable to 13NH3 (14% [13%; 16%] and 15% [14%; 16%] at 5 and 10 minutes postinjection, respectively).

| Table 1. Hemodynamic Parameters in Animals With and Without LAD Constriction |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                 | Rest                 | Stress                      | Rest                 | Stress                      | Ischemia                        |
| Heart rate, bpm                 | 90 (78; 101)         | 125 (112; 155)              | 80 (70; 87)         | 115 (100; 113)              | 73 (70; 87)                     |
| Systolic BP, mm Hg              | 69 (55; 84)          | 110 (84; 115)               | 78 (56; 91)         | 100 (85; 110)               | 73 (70; 79)                     |
| Diastolic BP, mm Hg             | 35 (20; 51)          | 30 (20; 61)                 | 32 (21; 51)         | 31 (20; 59)                 | 46 (40; 53)                     |
| RPP, mm Hg/s                    | 57 (41; 81)          | 145 (100; 165)              | 66 (39; 77)         | 110 (95; 130)               | 56 (48; 69)                     |

BP indicates blood pressure; RPP, rate pressure product.
Values are given as median (25th; 75th percentile).

Figure 4. Comparison of image quality between 18F-BMS (images averaged from 15 to 20 minutes after injection) and 13NH3 (images averaged from 5 to 10 minutes after injection) in a normal heart. Note the clear delineation of the LV due to a reduced background and blood pool signal in the 18F-BMS images.
The comparison of $^{18}$F-BMS activity 10 and 40 minutes postinjection in the defect areas of pigs with coronary constriction revealed no signs of redistribution or washout of the tracer. $^{18}$F-BMS activities in the remote and defect areas were 5.2% (0.2%; 8.8%) and 5.4% (1.0%; 9.1%) higher at 40 minutes than at 10 minutes ($P=0.51$). Under resting conditions, an increase of 10.8% (6.3%; 15%; $P=0.02$ versus stress) was found in the normal myocardium.

### Regional Tracer Distribution

In the normal heart, only small regional differences in the uptake of tracers at rest or stress were found (Figure 6; Table 3). A maximum of 2% to 5% difference was found in the PET data between different myocardial segments with either $^{13}$NH$_3$ or $^{18}$F-BMS. The cumulative $^{18}$F-BMS counts in tissue samples showed no regional differences between any segments.

### Validation of MBF

The regional $^{18}$F-BMS dynamic data acquired over a 10- and 20-minute period could be fitted with the 3-compartment model with high success rates of 80% (68%; 89%) and 84% (80%; 94%), respectively. The success rate with the 2-compartment model was only 55% (44%; 64%), because it failed to describe the high retention. The correlation between analyses with the data from 10 and 20 minutes was very good (slope 0.98, $r=0.97$, $P<0.001$). In the following section, MBF values obtained with $^{18}$F-BMS or $^{13}$NH$_3$, the

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**Table 2. Contrast Ratios of $^{13}$NH$_3$ and $^{18}$F-BMS at 10 Minutes After Injection (Myocardium/Blood, Myocardium/Liver, and Myocardium/Lung)**

<table>
<thead>
<tr>
<th></th>
<th>Myocardium/Blood</th>
<th>Myocardium/Liver</th>
<th>Myocardium/Lung</th>
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</thead>
<tbody>
<tr>
<td>$^{13}$NH$_3$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stress</td>
<td>1.5 (1.4; 2.2)</td>
<td>0.7 (0.4; 1.1)</td>
<td>1.7 (1.5; 2.8)</td>
</tr>
<tr>
<td>rest</td>
<td>2.7 (1.9; 2.9)</td>
<td>1.2 (0.7; 1.7)</td>
<td>2.3 (1.8; 3.4)</td>
</tr>
<tr>
<td>$^{18}$F-BMS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stress</td>
<td>5.8 (4.3; 7.4)</td>
<td>2.0 (1.4; 2.3)</td>
<td>6.3 (5.4; 7.4)</td>
</tr>
<tr>
<td>rest</td>
<td>4.3 (3.6; 5.1)</td>
<td>2.0 (1.1; 2.1)</td>
<td>4.7 (4.1; 5.0)</td>
</tr>
<tr>
<td>$^{18}$F-BMS/$^{13}$NH$_3$</td>
<td>2.9 (2.7; 4.3)</td>
<td>3.1 (2.1; 4.2)</td>
<td>3.4 (2.4; 4.4)</td>
</tr>
<tr>
<td>stress</td>
<td>1.8 (1.3; 2.4)</td>
<td>2.1 (0.9; 2.5)</td>
<td>2.0 (1.4; 2.7)</td>
</tr>
</tbody>
</table>

For all conditions, $^{18}$F BMS was superior to $^{13}$NH$_3$ as shown below. Values are given as median (25th; 75th percentile).

The comparison of $^{18}$F-BMS activity 10 and 40 minutes postinjection in the defect areas of pigs with coronary constriction revealed no signs of redistribution or washout of the tracer. $^{18}$F-BMS activities in the remote and defect areas were 5.2% (0.2%; 8.8%) and 5.4% (1.0%; 9.1%) higher at 40 minutes than at 10 minutes ($P=0.51$). Under resting conditions, an increase of 10.8% (6.3%; 15%; $P=0.02$ versus stress) was found in the normal myocardium.

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3-compartment model, and 20 minutes of dynamic data are reported. Mean MBF values obtained with $^{13}$NH$_3$ or $^{18}$F-BMS were comparable, although the $k_2$ of $^{18}$F-BMS (Table 4) was lower, which is consistent with the higher degree of myocardial tracer retention.

With the use of variable doses of stressor and LAD constriction, a wide range of regional flow values was achieved (0.1 to 3.0 mL · min$^{-1}$ · g$^{-1}$). The microsphere measurements confirmed reduced flow in the region of the constricted LAD compared with remote myocardium (62% [43%; 78%] of remote), which is reflected in the images (Figure 7) as well.

To correlate MBF measured with $^{18}$F-BMS and microspheres, all data points from rest and stress studies were combined (Figure 8). The data showed close agreement over the measured MBF range (slope 0.84, intercept 0.08, $r=0.88$, $P<0.001$; mean difference $-0.10 [-0.3; 0.1]$ mL · min$^{-1}$ · g$^{-1}$). Analysis of the regions perfused by the constricted LAD separately also revealed a good correlation but a reduced slope (slope 0.61, intercept 0.14, $r=0.93$, $P<0.001$; mean difference $-0.34 [-0.45; 0.08]$ mL · min$^{-1}$ · g$^{-1}$). The difference of the correlation slopes reached statistical significance ($P=0.016$). The defect extent size was modestly overestimated by $^{18}$F-BMS (slope 1.1, intercept 1.8, $r=0.63$, $P<0.001$).

**Discussion**

This study evaluated a novel $^{18}$F-labeled tracer, $^{18}$F-BMS-747158-02, for assessment of myocardial perfusion compared with $^{13}$NH$_3$ and microspheres in a pig model. We found that the new tracer provided good image quality and up to 3 times higher uptake ratios between the heart and lung, liver, or blood than $^{13}$NH$_3$. With microspheres as a “gold standard,” MBF was accurately quantified under rest and stress with the new tracer and a 3-compartment model.

Myocardial perfusion single-photon emission CT (SPECT) imaging is a well-accepted diagnostic test in nuclear cardiology, but it has limitations that result from suboptimal tracer characteristics in terms of tissue extraction and the lack of MBF quantification. The commercial availability of $^{82}$Rb as a PET perfusion tracer together with reimbursement of PET perfusion imaging has resulted in an increase of its clinical application.$^6$ $^{18}$ However, $^{82}$Rb is technically demanding owing to its short half-life, high count rates, and low myocardial extraction. Thus, an $^{18}$F-labeled flow tracer with fast and specific uptake would be advantageous.

<p>| Table 3. Differences (in Percent) Between $^{13}$NH$_3$ and $^{18}$F-BMS in the Normal Polar Maps |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Anterior</th>
<th>Septal</th>
<th>Inferior</th>
<th>Lateral</th>
<th>Apex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress 0.5 (−2.0; 3.6)</td>
<td>5.7 (3.2; 7.5)$^*$</td>
<td>2.9 (0.1; 7.1)$^*$</td>
<td>0.0 (−1.3; 1.1)</td>
<td>0.6 (−1.3; 2.4)</td>
</tr>
<tr>
<td>Rest −0.8 (−2.9; 2.6)</td>
<td>3.0 (0.2; 4.6)$^*$</td>
<td>4.2 (1.5; 5.7)$^*$</td>
<td>−1.1 (−3.4; 1.5)</td>
<td>−1.7 (−2.6; −0.7)$^*$</td>
</tr>
</tbody>
</table>

Values are given as median (25th; 75th percentile).

$^*$Significant difference.
18F-BMS showed homogeneously high and stable cardiac uptake, providing excellent image quality. We also found excellent target-to-background ratios consistent with recently published results in rats, rabbits, and primates.9,14,19 The ratios clearly exceeded those of 13NH3. The clinically important ratio between myocardium and liver was also clearly higher than that obtained with 18F-FBnTP, another recently introduced 18F-labeled tracer (1.8 versus 1.2) in a dog model.20 Although the ratios in the lungs (4.2 versus 12.2) and the blood (4.1 versus 12.2) were lower than those of 18F-FBnTP, they still exceeded those of 13NH3. Notably, it was also higher than those of the myocardium/liver ratio of SPECT tracers (0.7 to 1.4) in humans.21 These results confirm previous observations in small-animal models with use of a pig model that more closely resembles human heart in its size, heart rate, atrium; and LA, left atrium.

For details of the 3-compartment model, see Figure 1.

Figure 7. Corresponding short- and long-axis images and polar maps of 18F-BMS747158-02 before and after transient occlusion of the LAD demonstrating the clear delineation of territory with reduced blood flow. RV indicates right ventricle; RA, right atrium; and LA, left atrium.

Table 4. Results From Tracer Kinetic Modeling With a 3-Compartment Model

<table>
<thead>
<tr>
<th></th>
<th>Stress</th>
<th></th>
<th></th>
<th>Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MBF, mL·min⁻¹·g⁻¹</td>
<td>kurb, L/min</td>
<td>kurb·10³ L/min</td>
<td>MBF, mL·min⁻¹·g⁻¹</td>
</tr>
<tr>
<td>13NH3 20 min</td>
<td>1.8 (1.7; 1.9)</td>
<td>0.79 (0.78; 0.82)</td>
<td>7.5 (6.9; 7.8)</td>
<td>0.66 (0.64; 0.69)</td>
</tr>
<tr>
<td>18F-BMS 3C/20</td>
<td>1.9 (1.7; 2.0)</td>
<td>0.21 (0.20; 0.24)</td>
<td>12 (11; 12)</td>
<td>0.56 (0.51; 0.58)</td>
</tr>
<tr>
<td>18F-BMS 3C/10</td>
<td>2.0 (1.8; 2.1)</td>
<td>0.29 (0.28; 0.32)</td>
<td>13 (12; 13)</td>
<td>0.58 (0.54; 0.60)</td>
</tr>
<tr>
<td>18F-BMS 2C/2</td>
<td>1.6 (1.5; 1.7)</td>
<td>0.64 (0.59; 0.69)</td>
<td>N/A</td>
<td>0.57 (0.56; 0.61)</td>
</tr>
</tbody>
</table>

3C/20 indicates 3-compartment model including data until 20 minutes after injection; 3C/10, 3-compartment model including data until 10 minutes after injection; 2C/2, 2-compartment model 2 minutes after injection; and N/A, not applicable.

Values are given as median (25th; 75th percentile).

We found that total residual activity in the blood pool after 18F-BMS injection was comparable to that of 13NH3. The small increase in myocardial tracer uptake from 10 to 40 minutes both in rest and stress conditions is compatible with a not-yet-identified tracer metabolite. However, as shown for 13NH3, quantification of MBF does not require metabolite correction, and similarly, we did not use any correction when using 18F-BMS.15 Delayed uptake of 18F-BMS into the transiently ischemic area was recently reported in rats.23 This was not observed in the present model, in which tracer uptake remained stable in both ischemic and remote areas. This would not have affected quantitative MBF measurements, because only 10 or 20 minutes of data were used for modeling. The discrepancy between studies may be related to differences in protocols (2 hours versus 40 minutes between tracer injection and imaging) or species differences (rat versus pig) in metabolism and recirculation of the tracer and needs to be specifically addressed in future studies.

The absolute quantification of MBF with a 3-compartment model was highly reliable for both 10- and 20-minute acquisitions, whereas a simplified 2-compartment approach often failed owing to high tracer retention. The transition from semiquantitative to quantitative analysis of MBF involves complex mathematical modeling and depends on accurate assessment of blood and tissue signals. Therefore, quantitative data are more prone to artifacts, and areas always exist where the process fails. However, the excellent signal-to-noise ratios provided by 18F-BMS in conjunction with a robust software implementation represent an important step toward the direction of flow quantification. The present study is the first in vivo study demonstrating the feasibility of MBF quantification with 18F-BMS. Good agreement was found between MBF as assessed by radioactive microspheres and compartmental modeling in the investigated perfusion range. The observed correlation corresponds well to 13NH3 in a dog model.17 This finding also parallels the high flow-independent extraction of 18F-BMS observed in isolated rabbit24 and rat hearts9 and indicates that 18F-BMS is less affected by the “roll-off” phenomenon at high flow rates than 99mTc sestamibi, 82Rb, and 18F-FBnTP.20

A modest underestimation of MBF by 18F-BMS (slope 0.84) was noted, which could have been caused by several factors. Despite the small amount of tracer injected, overcorrection due to dead time losses in the tomograph could have resulted in overestimation of the input function. Furthermore, despite application of a validated partial volume correction, underestimation of myocardial count rates is possible. Although previous studies indicate high first-pass extraction, the possibility of an underestimation of tracer extraction in the kinetic modeling exists. In practice, correction factors can be applied to correct for underestimation of MBF by flow tracers.25 Compared with 82Rb with high correction factors,26 for example, the present results show modest and consistent underestimation, which indicates good properties of 18F-BMS.
for flow quantification. $^{18}$F-BMS tended to underestimate MBF in the areas of flow limitation caused by LAD constriction (slope 0.61). This could parallel the behavior of the mitochondria-targeting SPECT tracer $^{99m}$Tc sestamibi, which also showed decreased extraction in an acute occlusion/reperfusion model in rats. Further research is required to delineate $^{18}$F-BMS kinetics in hypoxic or ischemic myocardium in detail.

Although pharmacokinetics of the tracer need to be determined in humans, the present results verify the good image quality, stable kinetics, and high extraction over a wide flow range that indicate its suitability for clinical protocols similar to those used with $^{99m}$Tc-labeled tracers: The tracer could be injected during physical exercise, followed by postinjection PET. Because of the long half-life, protocols that involve rest/stress studies on separate days or validation of tracer reinitiation protocols, such as subtraction of the residual activity as done in the present study, is still required. Provided that MBF assessment can be improved, the need for performing rest/stress protocols would become less important, because stress MBF together with functional evaluation in gated rest images would provide diagnosis of restricted “maximal” MBF independent of coronary flow reserve measurements. Besides detection of ischemia, $^{18}$F-BMS viability
imaging in combination with 18F-fluorodeoxyglucose metabolic imaging could be a relevant option for PET centers that have 18F-fluorodeoxyglucose available. The initial comparison between 18F-BMS PET and microsphere-derived defects showed close agreement, which indicates the potential of 18F-BMS for infarct-size quantification.28 Although the radiation dose of imaging protocols is still under investigation, initial estimates in humans indicate effective doses (0.02 mSv/MBq) in the same range as with other PET tracers29 but considerably lower than with SPECT tracers (99mTc-MIBI 13 to 16 mSv and 99mTc-tetrofosmin 11 mSv).30

**Study Limitations**

We investigated 18F-BMS only in the myocardium of healthy pigs. A potential depression of mitochondrial complex I function could affect the tracer uptake in other disease processes such as in heart failure.31–33 Consequently, future investigations of 18F-BMS should include models of chronic cardiac disease or clinical studies in defined patient cohorts.

Owing to the long half-life of 18F, scan repetition is a potential problem, because the remaining activity from the first injection can interfere with data obtained after the second injection. We addressed this issue by regional background subtraction with data acquired immediately before a second injection. This approach minimizes the possibility of motion artifacts due to good image quality and could be suitable for clinical use.

**Conclusions**

18F-BMS is a promising new perfusion tracer with very high and specific myocardial uptake, up to a 3-fold increase in target-to-background ratio compared with 13NH3, and a linear relation to absolute perfusion values. Thus, the new tracer appears useful for detection of regional myocardial ischemia, as well as quantification of flow reserve and defect extent.

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**Disclosures**

Drs Yu, Robinson, and Casebier are employees of Lantheus Medical Imaging, North Billerica, Mass. The remaining authors report no conflicts.

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CLINICAL PERSPECTIVE

Because of its unique ability to quantify regional myocardial perfusion in absolute terms, positron-emission tomography (PET) provides high sensitivity for detection of coronary artery disease and allows evaluation of early abnormalities in coronary vasoreactivity in patients at risk. However, the short half-life, on the order of minutes, of typical myocardial blood flow PET tracers limits its clinical use, unless an on-site cyclotron is available. 18F-BMS-747158-02 is a novel 18F-labeled PET perfusion tracer that targets the mitochondrial complex. Its longer half-life allows distribution from a central cyclotron facility. In the present study, we evaluated its imaging properties in a large animal model using a clinical PET scanner and validated its use for quantification of myocardial blood flow using kinetic modeling. 18F-BMS-747158-02 PET provided excellent image quality that allowed accurate delineation of perfusion defects caused by transient constriction of a coronary artery. Ratios of 18F-BMS-747158-02 uptake between the heart and surrounding tissues, including liver, lung, and blood, were significantly higher than those of the current standard tracer, ammonia. Compared with the “gold standard,” microspheres, 18F-BMS-747158-02 PET proved to be highly accurate in measuring blood flow over a wide range of flow values under rest and pharmacological stress. Thus, 18F-BMS-747158-02 is a very attractive new PET perfusion tracer that provides excellent image quality and quantitative measures of regional myocardial perfusion. These, combined with its long tracer half-life, indicate that this tracer has potential in the clinical workup of patients with suspected or proven coronary artery disease.
Evaluation of the Novel Myocardial Perfusion Positron-Emission Tomography Tracer 18 F-BMS-747158-02: Comparison to 13N-Ammonia and Validation With Microspheres in a Pig Model

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