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Evaluation of a Novel ^{18}F-Labeled Positron-Emission Tomography Perfusion Tracer for the Assessment of Myocardial Infarct Size in Rats

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Background—The goal of this study was to evaluate a new ^{18}F-labeled positron-emission tomography (PET) perfusion tracer, ^{18}F BMS747158-02, for the assessment of myocardial infarct (MI) size.

Methods and Results—Wistar rats were studied 24 hours after ligation of the left coronary artery either permanently (n=15) or transiently (n=16) for 30 minutes. Seven nonoperated rats were studied as controls. The rats were injected with 37 MBq of ^{18}F BMS747158-02 and imaged with a small animal PET scanner for 20 minutes. Polar maps were generated for measurement of PET defect size, and left ventricular systolic and diastolic volumes were assessed in gated images. As a reference, MI size was determined by 2,3,5-triphenyltetrazolium chloride staining of left ventricular tissue samples. Permanent or transient ligation of the left coronary artery produced transmural or subendocardial MI of variable sizes, respectively. In normal rats, PET imaging demonstrated intense and homogeneous uptake of ^{18}F BMS747158-02 throughout the myocardium. After ligation, sharply defined perfusion defects were present. Throughout the imaging period, the defect size correlated closely with the MI size either after permanent (r=0.88; P<0.01; mean difference, 1.86%) or transient (r=0.92; P<0.01; mean difference, 2.16%) ligation of the left coronary artery. Moreover, reduction of left ventricular systolic function measured with PET correlated with the MI size (r=−0.81; P<0.01; n=23).

Conclusions—Myocardial ^{18}F BMS747158-02 PET imaging provides excellent image quality and uptake properties, enabling accurate evaluation of MI size and left ventricular function in rats. It is a promising technique for evaluation of MI size in clinical trials. **(*Circ Cardiovasc Imaging*. 2009;2:77-84.)**

Key Words: ^{18}F BMS747158-02 ■ cardiac PET ■ perfusion ■ myocardial infarction ■ TTC staining

Measurement of myocardial infarct (MI) size is an important clinical goal after an acute myocardial infarction (AMI) for prognostic assessment and evaluation of therapeutic interventions.[1] Nuclear imaging by single-photon emission tomography (SPECT) using ^{99m}Tc sestamibi, 99mTc tetrofosmin, or 201thallium, is extensively validated and considered as a widely used tool for the assessment of MI size.[1,2] It allows accurate measurement of myocardium at risk, final MI size, and myocardial salvage by reperfusion therapy. The extent and degree of irreversible myocardial tissue injury after an AMI are strong predictors of clinical outcomes and interventions that reduce injury and improve prognosis.[1–6] Thus, measurement of MI size allows risk stratification of patients and is an attractive surrogate end point instead of mortality for efficacy of therapeutic strategies in clinical trials.[1,2] However, technical limitations of SPECT imaging, such as a low spatial resolution and the assessment of only relative tracer inhomogeneities resulting from soft tissue attenuation or scatter, may compromise delineation of small infarcts and diagnostic accuracy of SPECT.[1,7]

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Positron-emission tomography (PET) is increasingly used to evaluate myocardial viability and detect coronary artery disease.[7] It has several technical advantages over SPECT, such as higher spatial resolution and owing to accurate attenuation correction, it can provide quantitative measures of myocardial tracer uptake.[7] However, short half-life of the PET tracers currently used for evaluation of myocardial blood

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flow; ^{13}N-ammonia, ^{82}Rubidium, and ^{15}O water limit its widespread clinical use, because of the need for nearby cyclotron or generator. Recently, the novel ^{18}F-labeled tracer, ^{18}F BMS747158-02, was characterized for evaluation of myocardial perfusion with PET.[8–10] Because of the half-life of 110 minutes, it can be distributed by a central cyclotron facility in a similar manner as ^{18}F fluoro-2-deoxy-D-glucose (FDG) facilitating its applicability for clinical imaging protocols. ^{18}F BMS747158-02 is an analogue of the insecticide pyridaben that binds the mitochondrial complex I of the electron transport chain with high affinity.[8] Thus, it shows selective uptake to the heart because of high density of mitochondria in the myocardium. Initial experimental studies have demonstrated excellent properties of ^{18}F BMS747158-02 for the assessment of myocardial perfusion by PET.[8–10] Image quality is not only excellent because it emits a lower energy positron that travels a shorter distance in tissue before annihilation, but the contrast between the heart and the surrounding organs are also high and stable over time. Furthermore, extraction of ^{18}F BMS747158-02 in the heart is high and sustained at different flow rates indicating suitability for quantification of blood flow reserve.[9,10] However, the value of ^{18}F BMS747158-02 in determination of MI size remains unknown. Development of high-resolution dedicated SPECT and PET scanners has made it possible to image MI size accurately in small animal models.[11–14,15]

In this study, we sought to validate ^{18}F BMS747158-02 PET for measurement of MI size using a small animal PET scanner in a rat model 24 hours after permanent or transient ligation of the left coronary artery (LCA). We studied regional uptake of ^{18}F BMS747158-02 and compared PET defect size with MI size measured by 2,3,5-triphenyltetrazolium chloride (TTC) staining of tissue samples. Moreover, we studied the feasibility of measuring left ventricular (LV) systolic function in cardiac-gated ^{18}F BMS747158-02 PET images by comparing it with MI size.

Statement of Responsibility

The authors have full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written. This final revised manuscript has been read, and each author's contribution has been approved by the appropriate author.

Methods

Animal Model

Fifty-two healthy male Wistar rats (Charles Rivers Laboratories Inc), weighing 331.2±84 g on average, were studied at the age of 8 to 10 weeks. They were divided into 3 groups; permanent ligation of the LCA (n=20) for 24 hours, ligation of LCA for 30 minutes followed by 24 hours of reperfusion (n=25) and nonligated controls (n=7). The average interval between LCA ligation and tracer injection was 24:10±0:55 hours. Ligation of the LCA was performed using the previously described method.[16] Briefly, the rats were anesthetized with intramuscular administration of midazolam (5 mg/kg), fentanyl (0.05 mg/kg), and medetomidin (0.5 mg/kg) and connected to a rodent ventilator. The heart was exposed through a left lateral thoracotomy of the fourth intercostal space, and the LCA was ligated near to its origin (≈2 to 3 mm from the tip of left atrium). Reperfusion was achieved by releasing the ligature. Successful coronary artery ligation was confirmed by pallor and reperfusion by a blush of the myocardium over the area at risk. The study protocols were approved by the regional governmental commission of animal protection (Regierung von Oberbayern, Germany).

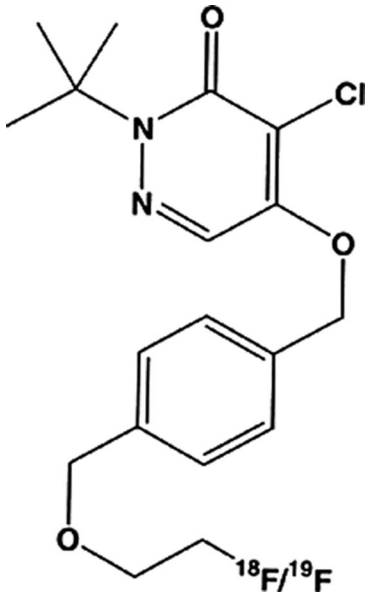

Figure 1. The chemical structure of ^{18}F BMS747158-02.

Tracer Preparation

^{18}F BMS747158-02 (Figure 1) was prepared following the described method.[9] In short, the dry cryptate ($[K_{c2.2.2.}]^{+}{}^{18}F^{-}$) was resolubilized with a solution of BMS747155-01 in dry acetonitrile. Then, the mixture was stirred at 90°C for 10 minutes and purified by preparative high-performance liquid chromatography. After the dilution, ^{18}F BMS747158-02 was immobilized on a reversed-phase cartridge, washed, and eluted with ethanol. The solvent was removed under reduced pressure. Finally, a quality control was performed with an analytic high-performance liquid chromatography system. The overall radiochemical yield was 50% to 60%, and the radiochemical purity ≥99%. The whole procedure takes less than 60 minutes to be ready for tracer injection.

PET Imaging

Imaging was performed in the prone position using an animal microPET scanner (Inveon Dedicated PET, Siemens Medical Solutions Inc). Rats were anesthetized using 1.5% isoflurane throughout the imaging. After starting image acquisition, rats were injected with an average of 27.4±6.7 MBq of ^{18}F BMS747158-02 over 15 seconds in the tail vein. The dynamic PET acquisition continued for 20 minutes in listmode format. ECG was registered using needle electrodes during imaging for the cardiac gating imaging.

PET Image Reconstruction

The PET data were sorted into 29 serial images consisting of 18×5-, 7×30-, 2×150-, and 2×300-second frames and reconstructed using a filtered backprojection algorithm with a cutoff at the Nyquist frequency. The resulting matrix was 128×128 pixels with 159 transverse slices. The actual pixel size was 0.39×0.39 mm, with a slice thickness of 0.8 mm. Data were normalized and corrected for randoms, dead time, and decay (ASIPro software in the PET image analysis). No corrections were made for attenuation or scatter. For analysis of the LV systolic and diastolic volumes, listmode data were sorted into 8 gates per cardiac cycle.

PET Image Analysis

Analysis of the PET images was performed using the ASIPro (Siemens Medical Solutions Inc) and MunichHeart software packages.[13,17]

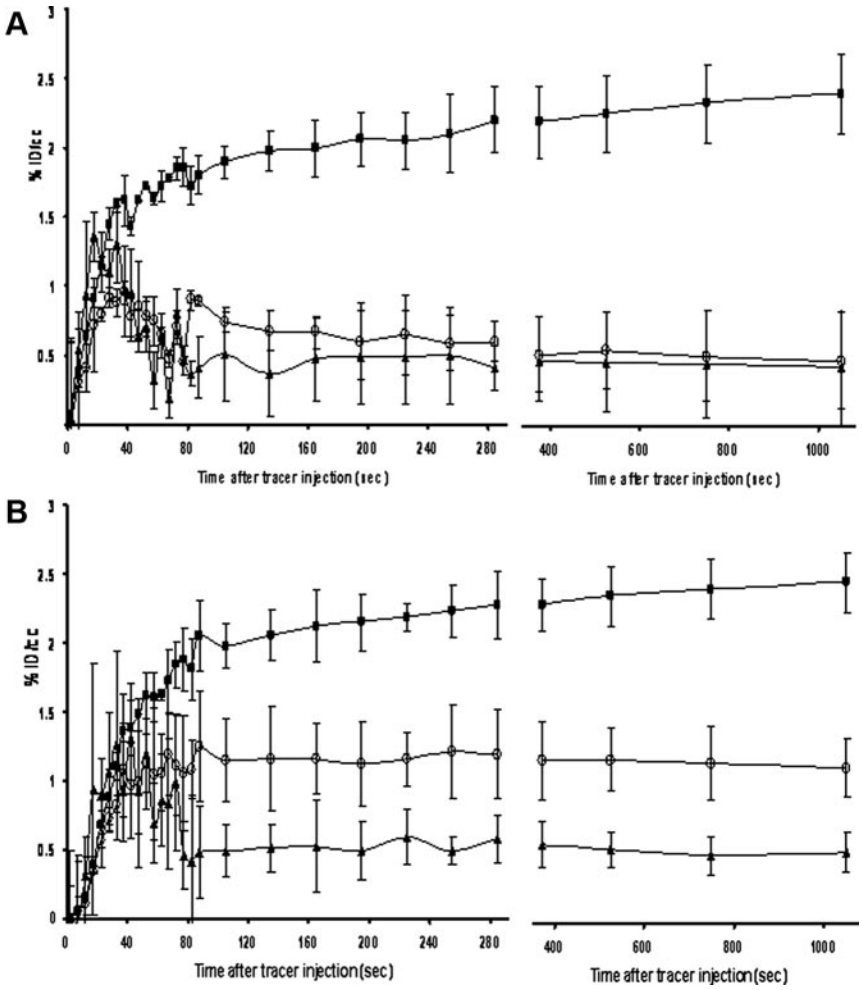

Figure 2. Time-activity curves of ^{18}F BMS747158-02 tissue uptake (%ID/mm3, mean±SD) in the remote, noninfarcted myocardium (■), defect area (○), and LV blood pool (▲) of rats with permanent (A; n=15) or transient (B, n=16) ligation of the LCA.

To compare tracer uptake in the infarcted and remote myocardium, regions of interest of equal size were drawn in the defect area and the myocardium opposite to it showing normal tracer uptake. For analysis of blood activity, a regions of interest was drawn in the LV blood pool. The Munich Heart software was used to generate myocardial contours and to ensure standardized delineation throughout the LV. The algorithm uses fully 3D sampling and geometric constraints to estimate the contours even with very little tracer uptake in the defect areas. Time-activity curves corrected for the injected dose of tracer were generated from the regions of interest in the remote, defect areas, and blood pool of each animal. The percentage of injected dose per tissue cubic centimeter (%ID/cm^3) in the PET images was calculated by normalization to a standard curve consisting of measurements of different amounts of activity (Figure 2).

For measurement of the average defect size, the tracer activities of each sampling point were displayed as a polar map. Each polar map was normalized to its maximum. The defect area was defined as the fraction of polar map elements with tracer uptake reduced for more than 50% of the maximum and expressed as percentage of the LV myocardium. The first 2 minutes after tracer injection were excluded from the summation of the images and the defect size analysis, because myocardial tracer activity had not yet reached a stable level. Then, time course of the defect size was compared at 2- to 5-, 5- to 10-, 10- to 15-, and 15- to 20-minute summed intervals after tracer injection. MI size using ^{18}F BMS747158-02 PET gated images was also measured through summation of 4 of 8 gates representing the diastolic intervals (the first and the last 3 gates).[18]

For analysis of the LV systolic function, the distribution of ^{18}F BMS747158-02 in the LV was extracted with the previously described algorithm using a volumetric sampling approach.[19] For volume analysis, the endocardial borders were estimated using a thresholding technique at 70% of peak counts within the wall profiles; and based on the endocardial contours, all endocardial volumes of the LV during the cardiac cycle were calculated. The frames with the largest and smallest volume were identified as end-diastole (ED) and end-systole (ES), respectively. The ejection fraction (EF) was calculated on the basis of volumes constructed from the ES and ED endocardial borders.[19]

Ex Vivo Histochemical Analysis

All animals were euthanized 20 minutes after tracer injection, immediately after the PET acquisition with an intravenous injection of 16% pentobarbiturate (Narcoren, Merial) at a dose of 150 mg/kg. The heart was excised. The LV was prepared by carefully removing the right ventricle, the atria, and the great vessels. The LV was then sliced along its short axis into four ≈1- to 2-mm slices from the apex to the base. The slices were weighted, incubated in 1% TTC solution at 37°C for 20 minutes, and both sides were photographed with a digital camera. The viable myocardium stained as red and the infarcted area stained as white were manually traced on both sides of each slice using ImageJ 1.38× software (National Institutes of Health). The MI size was then calculated as the percentage of infarcted myocardium from the total left ventricle.

Statistical Analysis

All data are expressed as mean±SD. Comparisons of ^{18}F BMS747158-02 uptake in the blood pool, remote myocardium, and defect area after permanent or transient LCA ligation were performed by either analysis of variances (ANOVA) followed by Bonferroni correction (multiple groups) or Student *t* test for unpaired or paired data (2 groups). ^{18}F BMS747158-02 uptake and MI size at

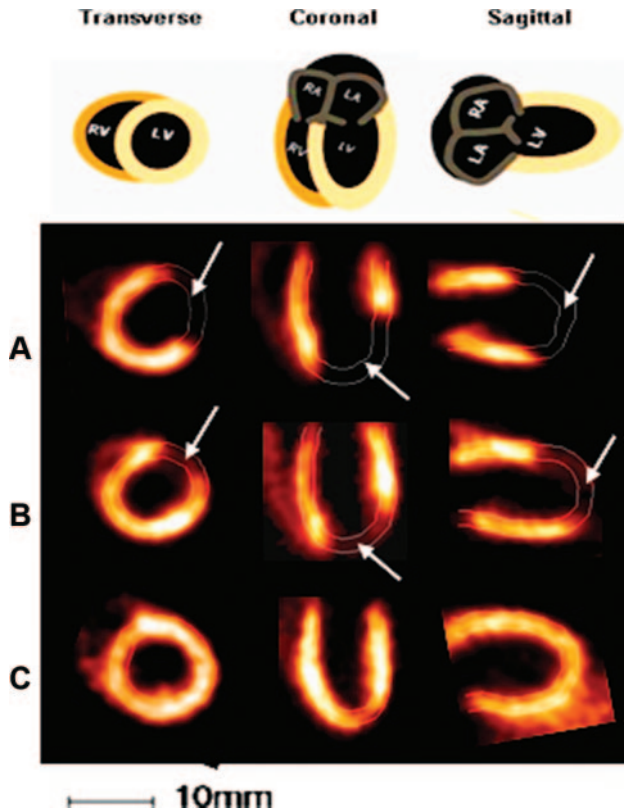

Figure 3. PET images of myocardial ^{18}F BMS747158-02 uptake (delineated) after permanent LCA ligation (A), transient LCA ligation (B), and in a control rat (C). Arrows point to perfusion defects.

different acquisition times were compared by ANOVA for repeated measurements. Linear regression analysis and Pearson's correlation between ^{18}F BMS747158-02 PET defect size and MI size were calculated, and the degree of agreement was analyzed using Bland-Altman analysis. Results were considered to be significant when the probability value was lower than 0.05.

Results

Survival of rats was 75% and 62% after permanent and transient LCA ligation, respectively. Thus, the final study group consisted of 15 animals with permanent LCA ligation, 16 animals with transient LCA ligation, and 7 nonoperated controls. By TTC staining, there were no infarctions in the controls. In contrast, all except 1 rat had MI after either permanent or transient ligation of the LCA (range, 0% to 53.7%). Although permanent ligation caused transmural MI in 11 of 15 (73%) rats, nontransmural infarctions were found in 12 of 16 (75%) of the reperfused hearts. The average MI size was 26.4±15.0% of the LV after permanent ligation and 17.9±14.8% after ischemia reperfusion. The coefficient of variation of repeated measurements of the MI size by 2 different observers was 6.7%.

PET Images

Representative ^{18}F BMS747158-02 PET images are shown in Figures 3 and 4. In the nonoperated rats, PET imaging demonstrated intense and homogeneous uptake of ^{18}F BMS747158-02 throughout the LV myocardium. In contrast, LCA ligation caused well-delineated perfusion defects of various sizes in anterolateral wall of the left ventricle. Region of infarcted myocardium in TTC staining matched well with the defect area in ^{18}F BMS747158-02 PET images (Figure 4).

Uptake in the Infarcted and Remote Myocardium

Time-activity curves of ^{18}F BMS747158-02 uptake normalized to the same injected dose demonstrated rapid and sustained uptake of ^{18}F BMS747158-02 in the remote, noninfarcted myocardium (Figure 2). Although activity remained stable from 5 minutes after injection in the defect areas and blood pool, there was still a small, continuous increase of activity in the remote myocardium (P=0.02).

The average tracer uptake in the remote myocardium of rats with either permanent or transient LCA ligation was comparable with that seen in controls (mean, 2.38±0.30%, 2.47±0.30%, and 2.60±0.40%, respectively). Compared with the remote myocardium, ^{18}F BMS747158-02 uptake in the defect areas of rats with either permanent or transient LCA ligation remained low throughout the imaging period (mean, 0.6%±0.2% and 1.2±0.3%; P=0.03). In the permanent LCA ligation group, uptake in the defect area was comparable to the blood pool, but slightly higher in the transient ligation group (P=0.04). Therefore, the average uptake in the remote myocardium was 4 times higher than that in the defect area of rats with permanent LCA ligation (P<0.01) and 2.1 times higher than that in the rats with transient ligation (P=0.03).

PET Defect Size and MI Size

Defect size determined by ^{18}F BMS-747158-02 PET images showed an excellent correlation with MI size determined by TTC staining (r=0.89; P<0.01; n=31). The correlation was equally good in rats with permanent (r=0.88; P<0.01; n=15) and transient (r=0.92; P<0.01; n=16) LCA ligation (Figure 5). Mean difference between ^{18}F BMS-747158-02

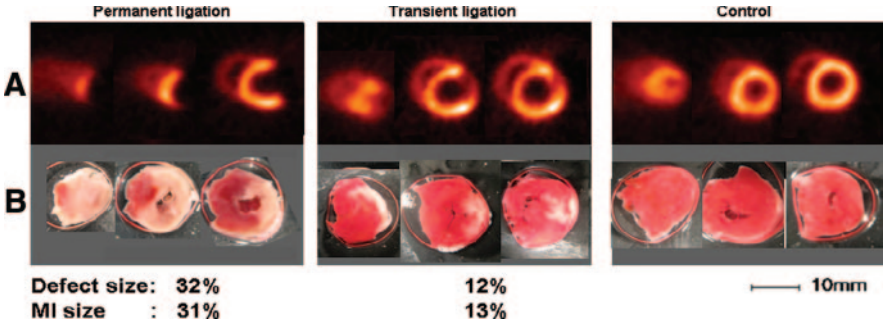

Figure 4. Short-axis PET images of myocardial ^{18}F BMS747158-02 uptake (A) and the corresponding myocardial slices from the level of infarction stained with TTC (B). Viable myocardium is stained red by TTC. The pictures are from the same animals as shown in Figure 3.

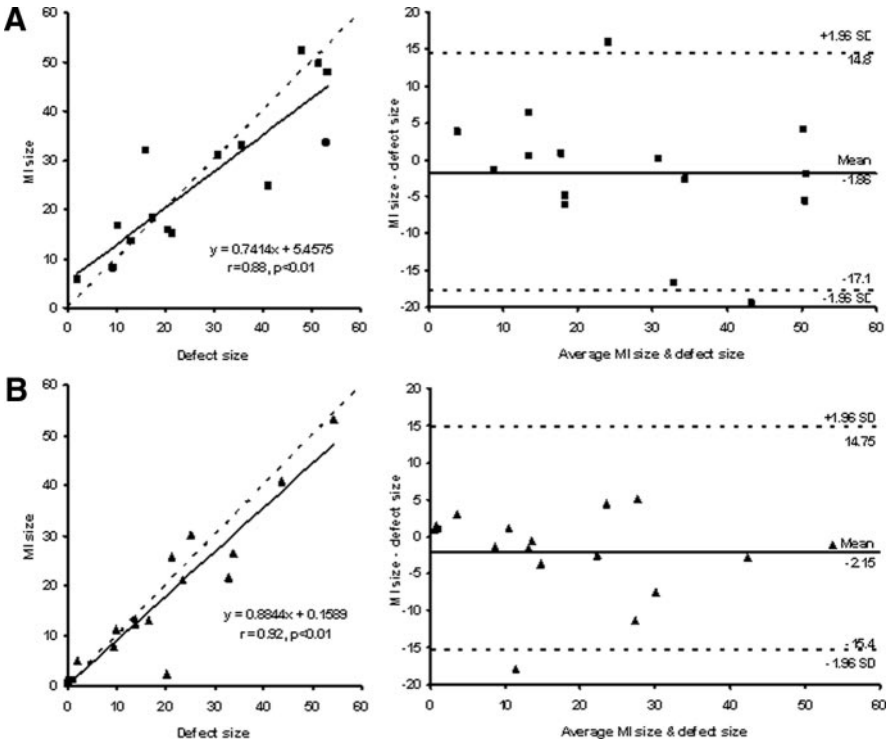

Figure 5. Correlation between ^{18}F BMS747158-02 PET defect size and MI size by TTC staining after permanent (A; n=15) and transient (B; n=16) LCA ligation.

PET defect size and MI size by TTC staining was 2.01%. The difference did not differ between the group with permanent and transient LCA ligation (1.86% versus 2.16%). Bland-Altman analysis demonstrated that the difference was similar, irrespective of MI size in both groups of permanent and transient LCA ligation (Figure 5). The coefficient of variation in repeated measurements of defect size by 2 independent observers was 7.6%, demonstrating high reproducibility. The defect size determined using the diastolic intervals of the gated PET images showed better correlation with the MI size (r=0.92; P<0.01; n=31; mean difference, 1.28%) than that of the nongated images. The correlation was good in rats with permanent (r=0.91; P<0.01; n=15; mean difference, 0.45%) and transient (r=0.93; P<0.01; n=16; mean difference, 2.11%) LCA ligation.

Defect Size at Different Time Points

Figure 6 demonstrates ^{18}F BMS747158-02 PET images and polar maps over time (2- to 5-, 5- to 10-, 10- to 15-, and 15- to 20-minute intervals after tracer injection). The PET defect remained constant over time after permanent and transient LCA ligation (P=0.67 and P=0.78, respectively) and was comparable over time with the true MI size (Table 1).

Assessment of Systolic Function

The automated measurement of the ES and ED volumes was done in the cardiac gated ^{18}F BMS747158-02 PET studies of 23 animals. We excluded 6 rats with permanent LCA ligation and 2 rats with transient LCA ligation. These rats showed an extensive defect size (>50% LV) with no^{18}F BMS747158-02 uptake in the defect area precluding the proper delineation of the LV endocardial border by the contour detection algorithm.

The average ES volume was 0.38±0.14, 0.25±0.13 and 0.15±0.11 mL after permanent LCA ligation (n=9), transient LCA ligation (n=14), and in controls (n=7), respectively. The average ED volume was 0.62±0.21, 0.53±0.22, and 0.37±0.23 mL after permanent LCA ligation, transient LCA

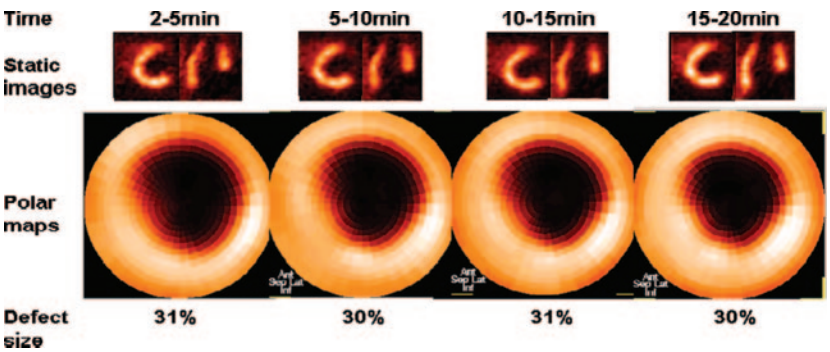

Figure 6. Static transverse and coronal ^{18}F BMS747158-02 PET images and polar maps demonstrating stable PET defect size over time using a 50% threshold after tracer injection in 1 animal with permanent LCA ligation.

Table. **^{18}F BMS-747158-02 PET Defect Size at Different Acquisition Times and MI Size**

	2–5 Minutes	5–10 Minutes	10–15 Minutes	15–20 Minutes	2–20 Minutes	MI Size
Permanent ligation	26.1±16.4%	27.1±18.0%	28.3±18.1%	28.8±19.0%	28.3±17.7%	26.4±15.0%
Mean difference to TTC	−0.34%	0.65%	1.87%	2.38%	1.86%	
Transient ligation	17.6±15.2%	18.7±15.8%	19.0±15.1%	20.5±16.6%	20.0±15.4%	17.9±14.8%
Mean difference to TTC	−0.31%	0.87%	1.1%	2.66%	2.16%	

ligation, and in controls, respectively. Thus, the average EF was 39.5±7.3%, 53.3±12.2%, and 61.1±13.4% after permanent LCA ligation, transient LCA ligation, and in controls, respectively. Coefficient of variation between EF measurements by 2 observers was 6.8%. The ES and ED volumes were significantly increased after permanent LCA ligation when compared with the controls ($P<0.05$, $P<0.05$), whereas EF was significantly reduced ($P=0.02$), respectively. However, the LV volumes and EF after transient LCA ligation were comparable with the controls.

The EF also showed good inverse correlations to the PET defect size and MI size ($r=-0.81$, $P<0.01$; and $r=-0.79$, $P<0.01$, n=23, respectively) (Figure 7).

Discussion

Our study demonstrates suitability of ^{18}F BMS747158-02, as a novel perfusion tracer targeting the mitochondrial complex 1, for evaluation of the acute ischemic myocardial injury by PET in rats. ^{18}F BMS747158-02 PET demonstrated excellent image quality that allowed accurate measurement of MI size after either permanent or transient coronary occlusion in comparison with TTC staining. Furthermore, systolic function measured in ECG gated ^{18}F BMS747158-02 PET images was inversely proportional to the size of MI. ^{18}F BMS747158-02 PET is a promising technique for accurate evaluation of MI size and assessment of LV function even in the presence of perfusion defects.

Previous studies using ^{18}F BMS747158-02 PET have shown excellent image quality that provided sharp delineation of perfusion deficits produced by acute ligation of the LCA for 2 hours.[10,20] We evaluated the feasibility of ^{18}F BMS747158-02 PET for quantification of MI size in a large group of rats with either permanent LCA ligation for 24 hours or transient LCA ligation for 30 minutes followed by 24 hours of reperfusion. Consistent with the previous studies, we uniformly found good image quality that allowed clear delineation of the borders of the defects ^{18}F BMS747158-02 PET images. Using polar maps with 50% threshold, we found an excellent match of the PET defect size and the true MI size as measured with TTC staining; a gold standard method for measuring size of both reperfused and nonreperfused MI.[21] The correlation was excellent even with just 2 to 5 minutes after tracer injection or when the defect size was assessed using the gated images.

In 4 of 31 rats (2 in permanent and 2 in temporary ligation group), the difference between the PET defect size and the true MI size was >10% (≈17%). The MI size in these 4 cases varied from 16.1% to 52.9% in TTC staining. In 3 of these 4 cases, the PET defect size underestimated the true MI size. We were not able to figure out a factor to explain these discrepancies, but considering the small size of the rat heart and the partial volume effects could result in overestimation of MI size. On the other hand, methodological issues related to tissue sampling procedure resulting in only few myocardial slices could be responsible for underestimation of MI size.

A previous study demonstrated redistribution of ^{18}F BMS747158-02 into the defect area when injected during a short (3 minutes) coronary artery occlusion that was not sufficient to induce detectable irreversible myocardial injury.[20] As shown by the time-activity curves, we found no ^{18}F BMS747158-02 uptake more than that seen in the blood pool in the region of transmural MI 24 hours after coronary artery occlusion. Compared with this, more uptake of ^{18}F BMS747158-02 was seen after transient LCA ligation. This uptake was most likely related to the presence of transmural infarction in the former (73% of cases) and nontransmural infarctions (75% of cases) with areas of preserved viability in the region of coronary artery occlusion in the latter. This, and the fact that ^{18}F BMS747158-02 PET defect size showed excellent correlation with MI size also in the presence of

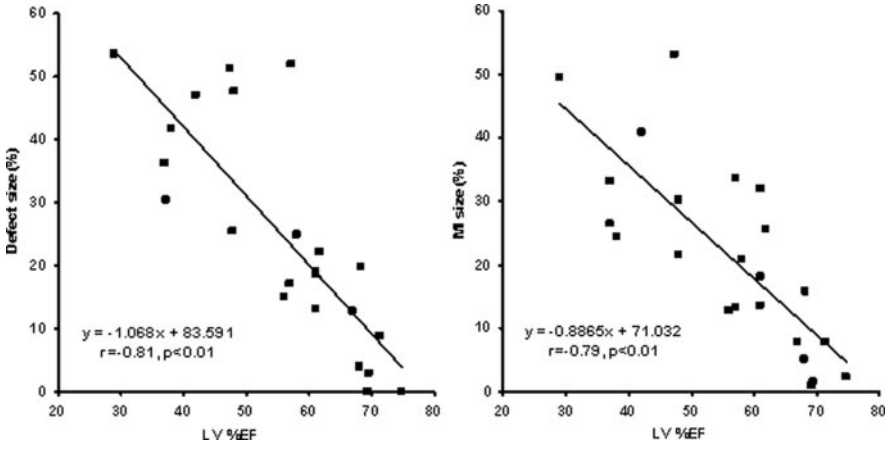

Figure 7. Correlation between ^{18}F BMS-747158-02 PET %EF and PET defect size (left) and MI size (right; n=23) by TTC.

reperfusion for 24 hours, indicates that ^{18}F BMS747158-02 is not retained in the irreversibly injured myocardium and provides specific differentiation of viable and acutely necrotic myocardial areas.

^{18}F BMS747158-02 PET defect size reflected MI size accurately throughout the 20-minute acquisition. There was only a small increase of 2% to 3% in the ^{18}F BMS747158-02 PET defect size toward the end of the study. Because ^{18}F BMS747158-02 activity in the ischemic region remained constant, increase in the defect size is most likely explained by a slight increase of activity in the remote, perfused myocardium toward the end of the study. This may have resulted in an increase in the measured defect size when 50% of the maximum activity in the remote myocardium was used as a threshold to define MI. Taking the very small increase of activity in the remote area and short duration of our imaging study into account, our results are still consistent with previous studies that provided evidence of stable tracer uptake in the normal myocardium when imaged until 2 hours from injection.[10,20] Therefore, ^{18}F BMS747158-02 PET may be useful for clinical evaluation of patients with suspected AMI. However, detailed kinetics of this new tracer over more prolonged time periods remains to be determined in future studies.

Dedicated, high-resolution nuclear and MRI imaging devices have been well established for evaluation of MI size in small animal models. Defect sizes in 99mTc sestamibi pinhole SPECT as well as in 13N ammonia PET have been shown to accurately reflect MI size in rats and mice.[12,14,15,22–25] Uptake of ^{18}F FDG, which is a marker of viable myocardium, has also been used to assess the MI size. As imaged with a small animal scanner, defect in ^{18}F FDG uptake in rats and mice correlates well with postmortem regional tissue activity concentrations[15]as well as MI size as measured with histological methods[11,13,14] or contrast-enhanced MRI imaging.[11,13] However, it should be noted that ^{18}F FDG uptake is influenced by metabolic conditions. Although viable myocardium shows highest uptake after insulin and glucose infusion, the infarcted area shows highest uptake in fasting conditions.[11,13] Although exact mechanisms are not known, this may be related to the presence of either inflammation or viable myocardium compromised by ischemia with enhanced glucose utilization in this area. ^{18}F BMS747158-02 compared favorably with perfusion tracer 13N ammonia in the sharpness of defect delineation as well as contrast ratios between myocardium and surrounding organs.[20] Algorithms for quantitative assessment of defect size in LV have been developed[16,26] and successfully applied for small animal studies.[11,13] Our results are consistent with previous studies in demonstrating excellent image quality for cardiac imaging with ^{18}F BMS747158-02 PET using a small animal scanner. Although overestimation of MI size with contrast-enhanced MRI using nonspecific Gadolinium chelates has been reported in some studies[27,28] such an effect was not seen with ^{18}F BMS747158-02 PET. In addition to being accurate, short-scan time made possible by excellent image quality and ease image analysis by automated software make ^{18}F BMS747158-02 PET an attractive method for monitoring MI size in the preclinical studies. Besides using MI as a surrogate end point, it might be important for interventional studies to assess infarct size early after ligation to compose groups of animals that match with respect to MI size.

Because our study was limited to AMI, further studies are needed to validate ^{18}F BMS747158-02 PET for detection of scars of chronic infarctions.

In addition to providing images of cardiac perfusion and metabolism, PET can be used to measure LV volumes and systolic function when gating techniques are applied.[29] Despite good image quality experience from gated PET studies in small animal models is limited,[30,31] we compared systolic function determined from gated ^{18}F BMS747158-02 PET images with MI size. Although MRI would have the most accurate reference method for validation of LV function measurement, it was not available for this study. Determination of LV volumes by ^{18}F BMS747158-02 was limited by difficulty of determining LV contours in the absence of visible tracer uptake in transmural MI. We did not use PET/CT imaging in our study. The anatomic information from the computed tomography would overcome this limitation. But despite this limitation, a good inverse correlation was found between LV EF measured with ^{18}F BMS747158-02 PET and the MI size. These preliminary observations demonstrate the feasibility of assessing LV wall motion using ^{18}F BMS747158-02 PET. Besides PET studies of blood flow, myocardial viability or MI size evaluation, the application of the cardiac gating techniques with PET imaging can provide a powerful way to noninvasive assessment of the impact of heart disease on ventricular function and remodeling.

Conclusion

Cardiac ^{18}F BMS747158-02 PET imaging provides excellent image quality, enabling accurate evaluation of MI size in rat models of both permanent coronary occlusion and ischemia reperfusion. Furthermore, analysis of LV volumes and systolic function was feasible. It may be a useful tool allowing accurate and comprehensive evaluation of MI in preclinical trials and a promising technique for evaluation of MI size in clinical trials.

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Disclosures

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References

1. Gibbons RJ, Valeti US, Araoz PA. The quantification of infarct size. *J Am Coll Cardiol*. 2004;44:1533–1542.

2. Schwaiger M, Melin J. Cardiological applications of nuclear medicine. *Lancet*. 1999;354:661–666.
3. Gersh BJ, Anderson JL. Thrombolysis and myocardial salvage. Results of clinical trials and the animal paradigm-paradoxic or predictable? *Circulation*. 1993;88:296–306.
4. Miller TD, Christian TF, Hopfenspirger MR. Infarct size after acute myocardial infarction measured by quantitative tomographic 99mTc sestamibi imaging predicts subsequent mortality. *Circulation*. 1995;92:334–341.
5. Schomig A, Kastrati A, Dirschinger J. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent versus thrombolysis for occluded coronary arteries in patients with acute myocardial infarction study investigators. *N Engl J Med*. 2000;343:385–391.
6. Kastrati A, Mehilli J, Dirschinger J; Stent versus thrombolysis for occluded coronary arteries in patients with acute myocardial infarction (STOPAMI-2) study. Myocardial salvage after coronary stenting plus abciximab versus fibrinolysis plus abciximab in patients with acute myocardial infarction: a randomised trial. *Lancet*. 2002;359:920–925.
7. Knuuti J, Bengel FM. Positron emission tomography and molecular imaging [Review]. *Heart*. 2008;94:360–367.
8. Yalamanchili P, Wexler E, Hayes M. Mechanism of uptake and retention of ^{18}F BMS-747158-02 in cardiomyocytes: a novel PET myocardial imaging agent. *J Nucl Cardiol*. 2007;14:782–788.
9. Huisman MC, Higuchi T, Reder S. Initial characterization of an ^{18}F-Labeled myocardial perfusion tracer. *J Nucl Med*. 2008;49:630–636.
10. Yu M, Guaraldi MT, Mistry M. BMS-747158-02: a novel PET myocardial perfusion imaging agent. *J Nucl Cardiol*. 2007;14:789–798.
11. Stegger L, Hoffmeier AN, Schafers KP. Accurate noninvasive measurement of infarct size in mice with high-resolution PET. *J Nucl Med*. 2006;47:1837–1844.
12. Liu Z, Kastis GA, Stevenson GD. Quantitative analysis of acute myocardial infarct in rat hearts with ischemia-reperfusion using a high-resolution stationary SPECT system. *J Nucl Med*. 2002;43:933–939.
13. Higuchi T, Nekolla ST, Jankaukas A. Characterization of normal and infarcted rat myocardium using a combination of small-animal PET and clinical MRI. *J Nucl Med*. 2007;48:288–294.
14. Thomas D, Bal H, Arkles J. Noninvasive assessment of myocardial viability in a small animal model: comparison of MRI, SPECT, and PET. *Magn Reson Med*. 2008;59:252–259.
15. Kudo T, Fukuchi K, Annala AJ. Noninvasive measurement of myocardial activity concentrations and perfusion defect sizes in rats with a new small-animal positron emission tomograph. *Circulation*. 2002;106:118–123.
16. Ott I, Keller U, Knoedler M. Endothelial-like cells expanded from CD34+ blood cells improve left ventricular function after experimental myocardial infarction. *FASEB J*. 2005;19:992–994.
17. Nekolla SG, Miethaner C, Nguyen N. Reproducibility of polar map generation and assessment of defect severity and extent assessment in myocardial perfusion imaging using positron emission tomography. *Eur J Nucl Med*. 1998;25:1313–1321.
18. Hoffman EJ, Phelps ME, Wisenberg G. Electrocardiographic gating in positron emission computed tomography. *J Comput Assist Tomogr*. 1979;3:733–739.
19. Hattori N, Bengel FM, Mehilli J. Global and regional functional measurements with gated FDG PET in comparison with left ventriculography. *Eur J Nucl Med*. 2001;28:221–229.
20. Higuchi T, Nekolla SG, Huisman MC. A new ^{18}F-labeled myocardial PET tracer: myocardial uptake after permanent and transient coronary occlusion in rats. *J Nucl Med*. 2008;49:1715–1722.
21. Schwarz ER, Somoano Y, Hale SL. What is the required reperfusion period for assessment of myocardial infarct size using triphenyltetrazolium chloride staining in the rat? *J Thromb Thrombolysis*. 2000;10:181–187.
22. Hirai T, Nohara R, Hosokawa R. Evaluation of myocardial infarct size in rat heart by pinhole SPECT. *J Nucl Cardiol*. 2000;7:107–111.
23. Wu MC, Gao DW, Sievers RE. Pinhole single-photon emission computed tomography for myocardial perfusion imaging of mice. *J Am Coll Cardiol*. 2003;42:576–582.
24. Maskali F, Franken PR, Poussier S. Initial infarct size predicts subsequent cardiac remodeling in the rat infarct model: an in vivo serial pinhole gated SPECT study. *J Nucl Med*. 2006;47:337–344.
25. Acton PD, Thomas D, Zhou R. Quantitative imaging of myocardial infarct in rats with high resolution pinhole SPECT. *Int J Cardiovasc Imaging*. 2006;22:429–434.
26. Chareonthaitawee P, Schaefers K, Baker CS. Assessment of infarct size by positron emission tomography and ^{18}F-fluoro-2-deoxy-D-glucose: a new absolute threshold technique. *Eur J Nucl Med Mol Imaging*. 2002;29:203–215.
27. Saeed M, Weber O, Lee R. Discrimination of myocardial acute and chronic (scar) infarctions on delayed contrast enhanced magnetic resonance imaging with intravascular magnetic resonance contrast media. *J Am Coll Cardiol*. 2006;48:1961–1968.
28. Oshinski JN, Yang Z, Jones JR. Imaging time after Gd-DTPA injection is critical in using delayed enhancement to determine infarct size accurately with magnetic resonance imaging. *Circulation*. 2001;104:2838–2842.
29. Yamashita K, Tamaki N, Yonekura Y. Quantitative analysis of regional wall motion by gated myocardial positron emission tomography: validation and comparison with left ventriculography. *J Nucl Med*. 1989;30:1775–1786.
30. Croteau E, Bénard F, Cadorette J. Quantitative gated PET for the assessment of left ventricular function in small animals. *J Nucl Med*. 2003;44:1655–1661.
31. Schäfers KP, Lang N, Stegger L. Gated listmode acquisition with the quadHIDAC animal PET to image mouse hearts. *Z Med Phys*. 2006;16:60–66.

CLINICAL PERSPECTIVE

Measurement of myocardial infarct size is an important clinical goal after an acute myocardial infarction for prognostic assessment as well as evaluation of therapeutic interventions. Positron-emission tomography (PET) is an accurate tool for the assessment of coronary artery disease and myocardial viability. However, the short half-life of the PET flow tracers currently used limits its clinical use because of the need for nearby cyclotron or generator. A novel ^{18}F-labeled radiotracer for the evaluation of myocardial perfusion and the assessment of myocardial infarct size with PET (^{18}F BMS747158-02) has been developed. The results of this experimental study showed that ^{18}F BMS747158-02 PET provides excellent image quality that allowed accurate measurement of infarct size after either permanent or transient coronary occlusion. Compared with the ex vivo 2-3-5-triphenyl tetrazolium chloride staining, there was a close correlation between the quantitative PET defect size and the true infarct size. Furthermore, analysis of left ventricular volumes and systolic function was feasible in the gated images. Myocardial ^{18}F BMS747158-02 PET imaging is a promising technique for evaluation of infarct size.