

Stable Delineation of the Ischemic Area by the PET Perfusion Tracer ^{18}F -Fluorobenzyl Triphenyl Phosphonium After Transient Coronary Occlusion

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^{18}F -fluorobenzyl triphenyl phosphonium (FBnTP) has recently been introduced as a myocardial perfusion PET agent. We used a rat model of transient coronary occlusion to determine the stability of the perfusion defect size over time and the magnitude of redistribution. **Methods:** Wistar rats ($n = 15$) underwent thoracotomy and 2-min occlusion of the left coronary artery (LCA), followed by reperfusion. During occlusion, ^{18}F -FBnTP (92.5 MBq) and ^{201}Tl -thallium chloride (0.74 MBq) were injected intravenously. One minute before the animals were sacrificed at 5, 45, and 120 min after reperfusion, the LCA was occluded again and 2% Evans blue was injected intravenously to determine the ischemic territory. The hearts were excised, frozen, and sliced for serial dual-tracer autoradiography and histology. Dynamic in vivo ^{18}F -FBnTP PET was performed on a subgroup of animals ($n = 4$). **Results:** ^{18}F -FBnTP showed stable ischemic defects at all time points after tracer injection and reperfusion. The defects matched the blue dye defect ($y = 0.97x + 1.5$, $R^2 = 0.94$, $y = \text{blue-dye defect}$, $x = ^{18}\text{F}$ -FBnTP defect). Count density analysis showed no defect fill-in at 45 min but slightly increased activity at 120 min (LCA/remote uptake ratio = 0.19 ± 0.02 , 0.19 ± 0.05 , and 0.34 ± 0.06 at 5, 45, and 120 min, respectively, $P < 0.05$). For comparison, ^{201}Tl showed complete redistribution at 120 min (LCA/remote = 0.42 ± 0.04 , 0.72 ± 0.03 , and 0.97 ± 0.05 at 5, 45, and 120 min, respectively, $P < 0.001$). Persistence of the ^{18}F -FBnTP defect over time was confirmed by in vivo dynamic small-animal PET. **Conclusion:** In a transient coronary occlusion model, perfusion defect size using the new PET agent ^{18}F -FBnTP remained stable for at least 45 min and matched the histologically defined ischemic area. This lack of significant redistribution suggests a sufficient time window for future clinical protocols with tracer injection remote from the scanner, such as in a stress testing laboratory or chest pain unit.

Key Words: autoradiography; animal imaging; cardiology (basic/technical); molecular imaging; PET

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PET myocardial perfusion imaging is increasingly entering the clinical arena as a highly accurate technique for the workup of coronary artery disease (1,2). When compared with standard SPECT, it provides better temporal and spatial resolution, higher sensitivity for tracer detection, and robust correction of attenuation artifacts (3,4). The currently established PET myocardial perfusion tracers include ^{82}Rb -rubidium chloride, ^{13}N -ammonia, and ^{15}O -water, but their short radioactive half-lives (76 s, 10 min, and 2.1 min, respectively) require expensive on-site production by a cyclotron or commitment to a dedicated generator. Additionally, a physical-exercise stress test is not practical because of the rapid decay of these tracers.

^{18}F -fluorobenzyl triphenyl phosphonium (FBnTP) is one of several recently introduced ^{18}F -labeled perfusion tracers. It is a cation with a mechanism of uptake similar to $^{99\text{m}}\text{Tc}$ -tetrofosmin and $^{99\text{m}}\text{Tc}$ -sestamibi and has shown promising properties such as high cardiac uptake and retention in animal models (5–8). Because of the 110-min half-life of ^{18}F , ^{18}F -FBnTP may help to overcome the limitations caused by the rapid decay of currently used perfusion PET tracers. Stress protocols using physical exercise may be feasible. However, stable uptake and a lack of early washout and redistribution would be necessary to allow sufficient time for the patient to be moved from the treadmill to the camera for imaging.

Accordingly, in this study we investigated the stability of ^{18}F -FBnTP uptake and the presence of washout and redistribution. For this investigation, we tested the tracer in a rat model of transient coronary occlusion.

MATERIALS AND METHODS

Animal Model

Fifteen Wistar rats were used in this investigation. The experimental protocol was approved by the Institutional Animal Care and Use Committee and conformed to the Guide for the Care and Use of Laboratory Animals (9).

Anesthesia was induced before the intervention and maintained during it using 1%–3% isoflurane and mechanical ventilation. Left thoracotomy was performed to expose the heart. A 7-0 polypropylene

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suture on a small curved needle was passed through the myocardium beneath the proximal portion of the left coronary artery (LCA). Both ends of the suture were passed through a small vinyl tube to produce a snare. Then, the LCA was occluded for 2 min by pulling both ends of the suture against the vinyl tube to tighten the snare (10–12). Tracer was injected via a tail vein during the coronary occlusion. Reperfusion was then obtained by release of the snare. The success of coronary occlusion and reperfusion was confirmed by visual identification of regional cyanosis of the myocardial surface in the risk area, followed by a blush. The short phase of ischemia was tolerated well by all animals.

Dual-Tracer Autoradiography

Dual-tracer autoradiography was performed to compare ^{18}F -FBnTP uptake and ^{201}Tl uptake at various times after transient ischemia. The experimental protocol is depicted in Figure 1A. Immediately after LCA occlusion, 92.5 MBq of ^{18}F -FBnTP, which was produced as previously described (13), and 0.74 MBq of ^{201}Tl -thallium chloride were injected via a tail vein (14). Two minutes after injection of the tracers during coronary occlusion, reperfusion was achieved. Groups of animals were studied at 5 min ($n = 3$), 45 min ($n = 4$), and 120 min ($n = 4$) after reperfusion. To determine the ischemic myocardial territory histologically, the LCA was occluded again using the same snare (which was left on the heart after the initial LCA occlusion), and 2 mL of Evans blue dye (2%) were injected via the tail vein just afterward. The rat was euthanized 1 min after the dye was injected. Then, the heart was removed, sliced into 20- μm short-axis sections, and placed on autoradiography plates (Multi Sensitive Phosphor Screens; Perkin Elmer). The first exposure began immediately and continued for 45 min in order to visualize ^{18}F -radioactivity. Three days later, after decay of ^{18}F , a second exposure was performed for 4 d to image the lower dose of ^{201}Tl (12,14). Additionally, photographs were taken of blue-dye-stained short-axis slices.

Images of blue-dye-stained short-axis slices were displayed side by side with autoradiographs of ^{18}F -FBnTP and ^{201}Tl . Region-of-interest analysis was used to determine the ratio of remote radioactivity to defect radioactivity at all time points for both tracers. Additionally, with ImageJ software (National Institutes of Health), defect size was measured planimetrically in 4 continuous slices and expressed as a percentage of the entire myocardial circumference. The ^{18}F -FBnTP defect was compared with the unstained area on blue-dye images as a reference.

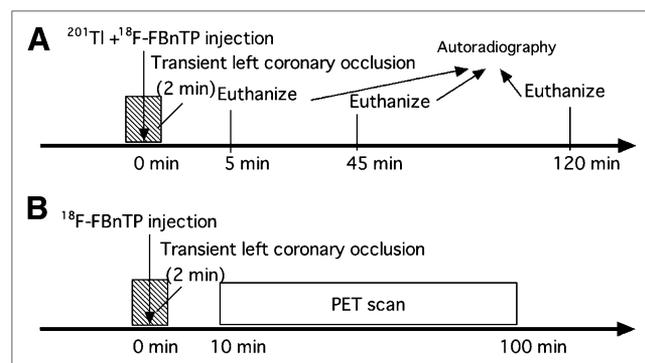


FIGURE 1. Schematic diagram of study protocols for dual-tracer autoradiography (A) and in vivo PET (B) in rat model of transient coronary occlusion.

Small-Animal PET

A dedicated small-animal PET scanner (eXplore VISTA; GE Healthcare) was used for in vivo imaging of ^{18}F -FBnTP kinetics. The protocol is outlined in Figure 1B. Intrinsic spatial and volume resolution of this system is reported as approximately 1.4 mm and 2.9 mm³, respectively (15). In 4 animals, 37 MBq of ^{18}F -FBnTP were injected during a 2-min LCA occlusion. The chest was closed rapidly after reperfusion had been achieved, and the animal was kept under anesthesia and placed on the scanner table immediately. A 90-min dynamic scan (10 min \times 9 frames) was started approximately 10 min after tracer injection. The acquired data were reconstructed with the standard VISTA algorithm (2-dimensional ordered-subsets expectation maximization). Reconstructed pixel sizes were 0.3875 mm and 0.775 mm in the transverse and axial directions, respectively. The dimensions of the reconstructed images were 175 \times 175 in each of the 61 transverse slices. Data were normalized and corrected for randoms, dead time, and decay. For quantification of the tracer signal, regions of interest were manually selected using AMIDE software (16). The defect area and contralateral remote area were identified in a midventricular short-axis image, and dynamic changes of average tracer activity in the region of interest between 10 and 90 min after tracer injection were determined.

Statistical Analysis

Data are presented as mean \pm SD. The Mann–Whitney *U* test was used to compare differences between 2 independent groups. Comparison of continuous variables between multiple groups was performed by ANOVA using ranks (Kruskal–Wallis test), followed by the Dunn multiple-contrast hypothesis test to identify differences between pairs of groups. The relationship between 2 variables was described using simple linear regression. A value of *P* less than 0.05 was considered statistically significant. Statistical analysis was done with StatMate III (ATMS Co., Ltd.).

RESULTS

Figure 2 shows representative images of autoradiography and blue-dye staining. At 5 min after reperfusion, autoradiography consistently showed uptake defects in the LCA territory for both ^{18}F -FBnTP and ^{201}Tl . With increasing time after reperfusion, the ^{201}Tl defect disappeared. At 120 min after reperfusion, no significant defect was identified, confirming the known redistribution phenomenon. Quantitatively, the LCA/remote uptake ratio for ^{201}Tl images was 0.42 ± 0.04 at 5 min, 0.72 ± 0.03 at 45 min, and 0.97 ± 0.05 at 120 min ($P < 0.01$ vs. 5 min). For ^{18}F -FBnTP, a clear uptake defect was found in the LCA occlusion territory until 120 min after reperfusion. The LCA/remote uptake ratio was 0.19 ± 0.02 at 5 min and remained unchanged at 0.19 ± 0.05 after 45 min, whereas there was only a mild reduction to 0.34 ± 0.06 at 120 min. LCA/remote uptake ratios were significantly higher for ^{18}F -FBnTP than for ^{201}Tl at all time points ($P < 0.05$ at 5, 45, and 120 min). There was a significant positive linear correlation between the defect size by ^{18}F -FBnTP and the size of the unstained vascular territory on blue-dye images ($P < 0.001$, $y = 0.97x + 1.5$, $R^2 = 0.94$, $y =$ blue-dye defect, $x =$ ^{18}F -FBnTP defect) (Fig. 3).

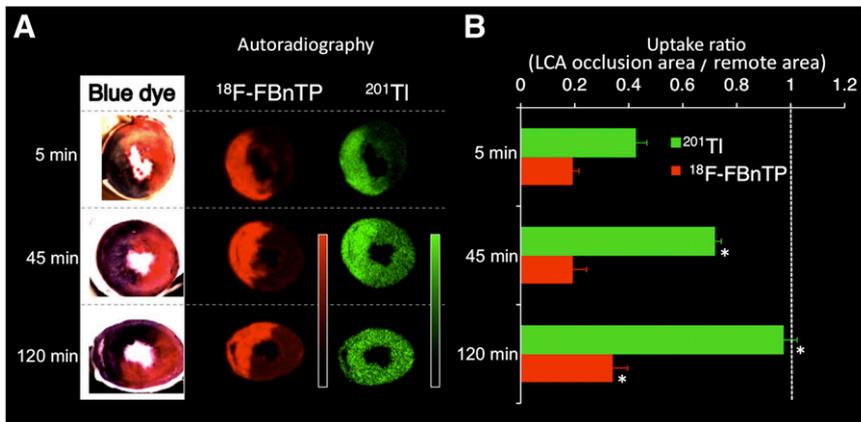


FIGURE 2. (A) Dual-tracer autoradiographic short-axis images and photographs of blue-dye staining at 3 different time points after tracer injection and reperfusion. ²⁰¹Tl (green) demonstrates complete redistribution at 120 min, but ¹⁸F-FBnTP (red) shows stable defect over time, delineating territory of LCA as confirmed by absence of blue dye. (B) Graph of uptake ratios for LCA occlusion area relative to remote area for both tracers at all 3 time points (**P* < 0.01 vs. 5 min).

In vivo PET confirmed the findings of autoradiography. Figure 4 shows serial short-axis dynamic PET images after ¹⁸F-FBnTP injection during short-term LCA occlusion, followed by reperfusion. The defect remained stable throughout the study period of 10–95 min after injection. Quantification of tracer uptake in the defect and remote area, as also shown in Figure 4, confirmed ¹⁸F-FBnTP stability and lack of washout or redistribution. LCA/remote uptake ratios were 0.36 ± 0.13 , 0.34 ± 0.14 , and 0.36 ± 0.16 at 15, 45, and 95 min after tracer injection, respectively.

DISCUSSION

We used a rat model of short-term coronary occlusion followed by reperfusion to study the kinetic properties of the ¹⁸F labeled myocardial perfusion agent ¹⁸F-FBnTP.

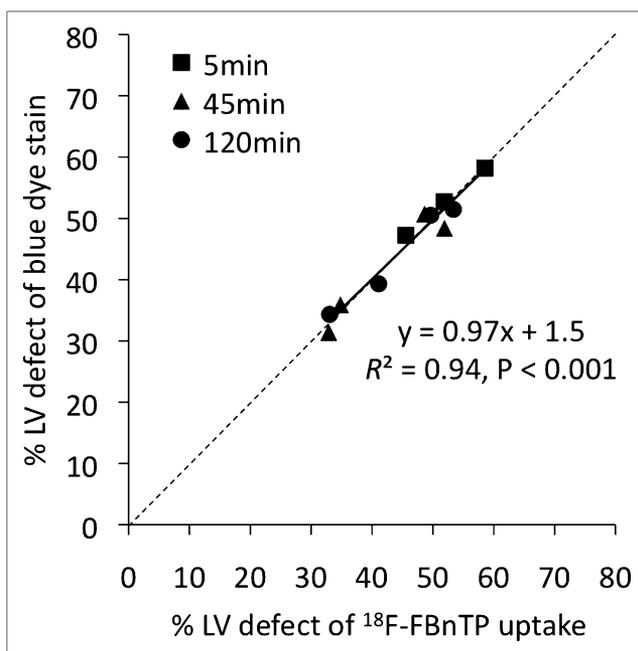


FIGURE 3. Regression plot for comparison between percentage defect area in ¹⁸F-FBnTP images and percentage blue-dye stain defect area.

Autoradiography and in vivo PET confirmed that this tracer, unlike ²⁰¹Tl-thallium chloride, shows a stable perfusion defect in the ischemic territory, without relevant washout or redistribution during the first 2 h after injection.

¹⁸F-FBnTP is a phosphonium cation that targets mitochondria via a membrane potential-dependent mechanism, similar to the commercially available ^{99m}Tc-labeled perfusion SPECT tracers ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin (5,6). In comparisons with ^{99m}Tc-tetrofosmin, a 2.7 times higher perfusion defect contrast and a superior, albeit still nonlinear, relationship between myocardial uptake and microsphere-determined flow were found in a dog model of coronary stenosis, indicating superior characteristics for myocardial perfusion imaging (7). Uptake remained stable in this study until 60 min after injection. Before this work, another study had already reported stable and homogeneous uptake in the heart of healthy dogs, with little in vivo metabolism of the agent (5). Additional in vitro ¹⁸F-FBnTP kinetic studies using isolated dog myocytes showed stable tracer binding for 120 min after resuspension in tracer-free solution (5).

The present study not only confirmed stable ¹⁸F-FBnTP distribution without redistribution, comparable to ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin (17), but also added new information to prior work. First, it showed that ¹⁸F-FBnTP detects perfusion defects accurately in rats, using small-animal imaging, whereas prior results were obtained in dogs. Second, it validated the size of the ¹⁸F-FBnTP perfusion defect against ex vivo blue-dye staining of the ischemic area. And third, it compared ¹⁸F-FBnTP with ²⁰¹Tl and showed superior separation between ischemic and remote areas, as well as absence of redistribution for ¹⁸F-FBnTP. The difference of separation even at the early time points (5 min) might be caused by a lack of ¹⁸F-FBnTP redistribution and a rapid ²⁰¹Tl redistribution into the ischemic area. A small decline in the defect-to-remote ratio for ¹⁸F-FBnTP at 120 min after injection was most likely overrated by a decay of ¹⁸F radioactivity and redistribution into the ischemic area of spillover from coinjected ²⁰¹Tl for dual-tracer autoradiography. Such spillover effects are unlikely at earlier time points because of the 125-fold difference in

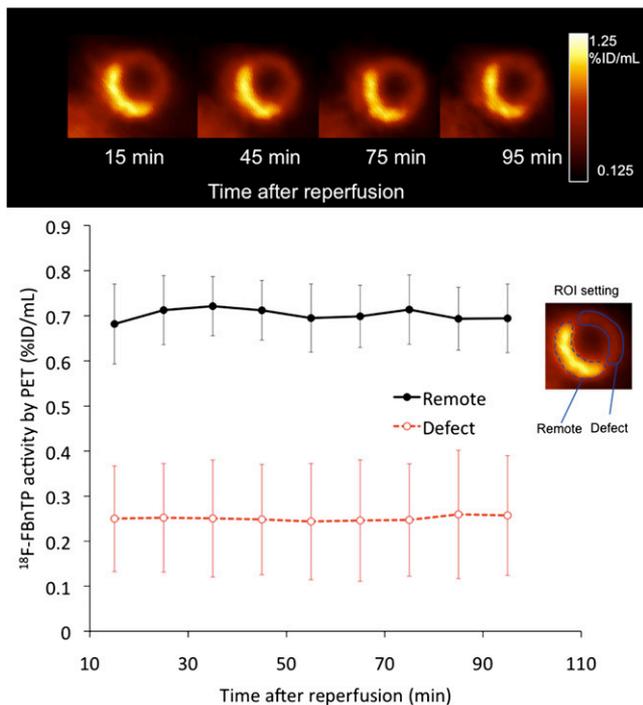


FIGURE 4. Representative short-axis small-animal PET images of ^{18}F -FBnTP at different time points after tracer administration during short-term occlusion, followed by reperfusion. Graph shows mean uptake in defect and remote area. %ID = percentage injected dose; ROI = region of interest.

radioactivity between the 2 tracers at the time of injection. This conjecture is supported by the additional *in vivo* PET study that did not show any significant redistribution over the study period of 110 min. Because other cationic tracers such as $^{99\text{m}}\text{Tc}$ -sestamibi are known to redistribute over time to some degree (18), further confirmatory studies in different experimental models might be necessary to conclude the absence of redistribution.

The results of our study (i.e., the stability of the perfusion defect and the absence of redistribution) suggest—for future clinical protocols—that ^{18}F -FBnTP will allow sufficient time for the patient to be moved from a treadmill to the PET camera for poststress imaging. The ability to perform physical-exercise stress perfusion PET with this longer-lived PET agent may be a future clinical advantage.

Our study also enabled a comparison of ^{18}F -FBnTP with another ^{18}F -labeled perfusion tracer, ^{18}F -BMS-747158-02. ^{18}F -BMS-747158-02, an analog of the insecticide pyridaben, has promising characteristics as a myocardial perfusion tracer (19–22). Unlike ^{18}F -FBnTP, ^{18}F -BMS-747158-02 is already undergoing clinical trials. It has recently been evaluated in a similar model of transient ischemia and reperfusion in rats, where, in contrast to ^{18}F -FBnTP in the present study, continuous slow tracer redistribution was found over 120 min (10). This difference may be a result of different uptake mechanisms. ^{18}F -BMS-747158-02 targets mitochondrial complex I (21,22), whereas ^{18}F -FBnTP targets mitochondrial membrane potential (8). Whether this observation

can be translated across species and has implications for clinical application of both agents remains to be determined.

Some limitations of the present study should be considered. First, although our results suggest that physical exercise may be an option in clinical studies because of stable uptake and lack of redistribution, our study was an experimental study in a rodent model. Early clinical applications will be necessary to show that ^{18}F -FBnTP is useful for imaging myocardial perfusion in humans and to confirm the lack of redistribution. And second, we used a model of tracer injection during temporary coronary artery occlusion followed by immediate reperfusion. This model was well suited to determine perfusion defect size but is not identical to the clinical situation, in which hemodynamically relevant stenosis is unmasked by a stress-induced increase of myocardial blood flow. The present model, however, has been well established in prior work (10). Additionally, the success of restoration of perfusion in the LCA area without irreversible tissue damage was confirmed not only by the restoration of color and wall motion of the heart during the procedure but also by the redistribution of coinjected ^{201}Tl .

CONCLUSION

^{18}F -FBnTP is a new PET tracer for assessment of myocardial perfusion abnormalities that shows stability of tracer uptake after injection, a lack of redistribution, and accurate delineation of the flow defect area. These characteristics suggest that exercise stress perfusion PET protocols may be possible in future clinical applications, similar to protocols currently used for SPECT with technetium-labeled agents.

DISCLOSURE STATEMENT

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