

Will ^{18}F flurpiridaz replace ^{82}Rb rubidium as the most commonly used perfusion tracer for PET myocardial perfusion imaging?

Dennis A. Calnon, MD, MASNC^a

^a OhioHealth Heart and Vascular Physicians, Columbus

Received Nov 28, 2017; accepted Nov 28, 2017

doi:10.1007/s12350-017-1153-z

See related article, pp. 2018–2030

Over the past two decades, there has been steadily growing interest in positron emission tomography (PET) myocardial perfusion imaging (MPI) as an alternative to single-photon emission computed tomography (SPECT) MPI for assessment of coronary artery disease (CAD). The feasibility of PET MPI has been enhanced by the availability of on-site ^{82}Rb rubidium (^{82}Rb) generators, eliminating the need for an on-site cyclotron.

CLINICAL ADVANTAGES OF ^{82}Rb PET MPI COMPARED TO CONVENTIONAL SPECT MPI

1. Lower radiation exposure for patients and laboratory personnel¹
2. Measurement of absolute myocardial blood flow and myocardial blood flow reserve (MBFR)
3. Measurement of regional and global myocardial systolic function at peak-stress (rather than post-stress as is done with SPECT MPI)²
4. Efficient (30 minute) rest-stress imaging protocol
5. Robust attenuation and scatter correction with superior diagnostic accuracy.³

The low radiation exposure is a result of the very short (76 second) half-life of ^{82}Rb . Radiation exposure for laboratory personnel is also extremely low for ^{82}Rb PET MPI as the entire protocol is performed in the PET camera, and the stress laboratory personnel and nuclear

technologists can monitor the procedure from a shielded control room. There is negligible residual radioactivity present after the ^{82}Rb study, which eliminates the radiation exposure to other medical personnel who are in close proximity to the patient (e.g., a sonographer who performs a transthoracic echocardiogram immediately following the PET MPI study).

The short half-life of ^{82}Rb also facilitates a rapid rest-stress imaging protocol. Equivalent ^{82}Rb doses can be administered for rest and peak-stress images (ensuring high quality for both sets of images), without the need to delay the peak-stress ^{82}Rb infusion or increase the peak-stress dose to compensate for residual resting tracer activity.

DISADVANTAGES OF ^{82}Rb AS A PET PERFUSION TRACER

However, the short half-life of ^{82}Rb poses challenges as well.

1. ^{82}Rb PET MPI is only feasible with pharmacologic stress, as there is rapid decay of ^{82}Rb activity and insufficient time to transfer the patient from a treadmill to the PET camera for post-exercise image acquisition.
2. The rapid decay of ^{82}Rb makes it impossible to repeat image acquisition in the event of patient motion. If severe patient motion artifact occurs on a peak-stress ^{82}Rb image, it is necessary to repeat the pharmacologic stress infusion as well as the ^{82}Rb infusion.

There are other limitations to the use of ^{82}Rb as a perfusion tracer for PET MPI.

1. The $^{82}\text{Sr}/^{82}\text{Rb}$ generator poses a large financial burden on the nuclear cardiology laboratory and limits ^{82}Rb PET MPI to laboratories with sufficient patient volume to justify the high ongoing operating costs.

Reprint requests: Dennis A. Calnon MD, MASNC, OhioHealth Heart and Vascular Physicians, Columbus dennis.calnon@ohiohealth.com
J Nucl Cardiol 2019;26:2031–3.

1071-3581/\$34.00

Copyright © 2018 American Society of Nuclear Cardiology.

2. Although ^{82}Rb is an analog of potassium and is actively transported via the Na^+/K^+ ATPase pump (like ^{201}Tl , a SPECT perfusion tracer with favorable myocardial uptake properties), the myocardial extraction fraction of ^{82}Rb has been reported to be lower than that of other PET perfusion tracers.⁴ The lower myocardial extraction fraction leads to an earlier plateau in myocardial tracer uptake during vasodilator stress and an underestimation of the blood flow disparity between normally perfused and hypoperfused myocardial regions. The clinical implication is an underestimation of the extent and severity of CAD by ^{82}Rb PET MPI.
3. The positrons produced by decay of ^{82}Rb are higher in energy than the positrons produced by other PET radionuclides, resulting in a longer positron range (the average distance traveled by a positron before interacting with an electron).⁵ The impact of the longer positron range of ^{82}Rb is poorer spatial resolution of ^{82}Rb PET images compared to images obtained using radionuclides with a shorter positron range (e.g., ^{13}N and ^{18}F).

Because of the limitations of ^{82}Rb as a PET perfusion tracer, there has been interest in developing novel perfusion tracers for PET MPI. ^{18}F flurpiridaz is a promising ^{18}F -labeled PET perfusion tracer in clinical development.^{6,7}

FAVORABLE PROPERTIES OF ^{18}F FLURPIRIDAZ AS A PET PERFUSION TRACER

1. The longer half-life of ^{18}F (108 minutes) permits unit dose delivery of ^{18}F flurpiridaz from a regional cyclotron and eliminates the need for an on-site cyclotron or an on-site $^{82}\text{Sr}/^{82}\text{Rb}$ generator. Unit dose delivery (depending on the price per dose) might represent an important economic advantage of ^{18}F flurpiridaz, eliminating one of the major obstacles preventing nuclear cardiology laboratories from performing PET MPI at present.
2. The short positron range of ^{18}F results in superior spatial resolution and takes full advantage of the excellent intrinsic spatial resolution of PET. The superior spatial resolution of ^{18}F flurpiridaz might improve the ability to resolve small areas of reduced myocardial perfusion and improve detection of branch vessel stenoses.
3. The longer half-life of ^{18}F would facilitate the use of treadmill exercise as an alternative to pharmacologic stress for PET MPI.
4. In the event of severe patient motion artifact, the longer half-life of ^{18}F would allow for repeat image

acquisition without the need to repeat the tracer injection or the pharmacologic stress agent infusion.

5. The very high myocardial extraction fraction of ^{18}F flurpiridaz⁸ might improve detection of mild to moderate (but functionally significant) coronary artery stenoses. In theory, ^{18}F flurpiridaz should provide a more accurate assessment of the true extent and severity of CAD compared to perfusion tracers with a lower myocardial extraction fraction (e.g., ^{82}Rb).

In this issue of the Journal, Dr. Maddahi and colleagues report data regarding the safety, tolerability, biodistribution, and radiation dosimetry of ^{18}F flurpiridaz when injected during exercise or adenosine stress in 12 normal healthy volunteers. The information is very timely as a phase 3 clinical trial of ^{18}F flurpiridaz is soon to begin. The authors concluded that ^{18}F flurpiridaz was well tolerated and that the radiation dosimetry was within the clinically acceptable range. The mean effective dose for ^{18}F flurpiridaz was 0.015 mSv/MBq for exercise stress and 0.019 mSv/MBq for adenosine stress. The dosimetry for resting ^{18}F flurpiridaz was reported previously.⁹

There are a few considerations regarding the applicability of the present study to patients referred for clinically indicated PET MPI.

1. The study population was small (12 subjects), predominantly male (10 of 12 subjects), normal body weight (BMI 20–29), healthy, and taking no medications. This patient population is very different from the population of patients referred for clinically indicated PET MPI. While it is understandable that young healthy volunteers are convenient subjects for a demanding and time-consuming phase 1 study, the potential impact of this healthy young study population (i.e., lower risk for adverse events) needs to be considered.
2. The study was limited to exercise and adenosine stress, and therefore, the biodistribution and radiation dosimetry results cannot be directly extrapolated to dipyridamole stress, regadenoson stress, dobutamine stress, or any of the vasodilator stress agents combined with low-level treadmill exercise.
3. The study was performed using 2D (with collimation) rather than 3D (without collimation) PET MPI. There is potential for using lower ^{18}F flurpiridaz tracer doses with a 3D imaging protocol.
4. The authors were not able to provide information regarding the radiation exposure to laboratory personnel with ^{18}F flurpiridaz compared to ^{82}Rb . Given the long half-life of ^{18}F , there will be potential for

higher radiation exposure to laboratory personnel and other medical staff in the facility. This concern needs to be addressed, and potential solutions to minimize exposure to medical staff should be explored (e.g., shielded waiting rooms might be needed for patients undergoing ^{18}F flurpiridaz PET MPI, and 3D PET imaging protocols should be developed to reduce ^{18}F flurpiridaz dosing).

In the end, the feasibility of exercise stress may not emerge as an important clinical advantage of ^{18}F flurpiridaz, as measurement of peak-exercise myocardial blood flow (and MBFR) would be technically challenging and would likely require alternative blood flow quantitative methods that do not depend on initiation of imaging prior to appearance of the tracer.¹⁰ The PET MPI imaging protocols for ^{18}F flurpiridaz will likely be less efficient than the protocols for ^{82}Rb , with proposed delays of 60 minutes and 30 minutes between the resting and peak-stress images for exercise and adenosine stress, respectively.⁹ Therefore, a rest-stress ^{18}F flurpiridaz protocol duration will undoubtedly exceed the duration of a rest-stress ^{82}Rb PET MPI protocol.

When considering the advantages and disadvantages of ^{82}Rb and ^{18}F flurpiridaz as tracers for PET MPI, there are many factors to consider, including protocol efficiency, radiation exposure to patients and laboratory personnel, diagnostic capabilities, protocol flexibility, and cost of the tracer. Will ^{18}F flurpiridaz replace ^{82}Rb rubidium as the most commonly used perfusion tracer for PET MPI? Only time will tell.

Disclosures

Dr. Calnon serves on the advisory board for Talaria Therapeutics, Inc. and as a consultant for Navidea Biopharmaceuticals, Inc.

References

1. Cerqueira MD, Allman KC, Ficaro EP, Hansen CL, Nichols KJ, Thompson RC, et al. Recommendations for reducing radiation exposure in myocardial perfusion imaging. *J Nucl Cardiol.* 2010;17:709–18.
2. Dorbala S, Hachamovitch R, Curillova Z, Vangala D, Kwong RY, DiCarli MF. Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. *JACC Cardiovasc Imaging.* 2009;2:846–54.
3. McArdle BA, Dowsley TF, Dekemp RA, Wells GA, Beanlands RS. Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease? A systematic review and meta-analysis. *J Am Coll Cardiol.* 2012;60:1828–37.
4. Lortie M, Beanlands RS, Yoshinaga K, Klein R, Dasilva JN, Dekemp RA. Quantification of myocardial blood flow with ^{82}Rb dynamic PET imaging. *Eur J Nucl Med Mol Imaging.* 2007;34:1765–74.
5. Garcia EV, Galt JR, Faber TL, et al. Principles of nuclear cardiology imaging. In: Dilsizian V, Narula J, editors. *Atlas of Nuclear Cardiology.* 4th ed. New York: Springer; 2013. p. 1–53.
6. Yu M, Guaraldi MT, Mistry M, et al. BMS747158-02: A novel PET myocardial perfusion imaging agent. *J Nucl Cardiol.* 2007;14:789–98.
7. Nekolla SG, Reder S, Higuchi T, et al. Evaluation of the novel myocardial perfusion PET tracer ^{18}F -BMS747158-02: comparison to ^{13}N ammonia and validation with microspheres in a pig model. *Circulation.* 2009;119:2333–42.
8. Huisman MC, Higuchi T, Reder S, et al. Initial characterization of an ^{18}F -labeled myocardial perfusion tracer. *J Nucl Med.* 2008;49:630–6.
9. Maddahi J, Czernin J, Lazewatsky J, et al. Phase I, first-in-human study of BMS747158, a novel ^{18}F -labeled tracer for myocardial perfusion PET: dosimetry, biodistribution, safety, and imaging characteristics after a single injection at rest. *J Nucl Med.* 2011;52:1490–8.
10. Sherif HM, Nekolla SG, Saraste A, et al. Simplified quantification of myocardial flow reserve with flurpiridaz F 18: validation with microspheres in a pig model. *J Nucl Med.* 2011;52:617–24.