

Rubidium-82 myocardial perfusion PET/CT

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Summary

Scholtens AM, Barneveld PC. Rubidium-82 myocardial perfusion PET/CT.

Myocardial perfusion imaging (MPI) with Technetium-based compounds is the mainstay for nuclear cardiology in the Netherlands based primarily on its availability, with PET MPI only performed in certain hospitals with cyclotron-generated radiopharmaceuticals such as N-13 ammonia or O-15 water. In recent years, Rubidium-82 (a generator-based positron emitter) PET has become the standard modality for MPI in two hospitals in the Netherlands: the Jeroen Bosch Hospital and the Meander Medical Center. In this article we describe the general aspects of imaging with this tracer.

Introduction

Historically and into the present day, single photon emission computed tomography (SPECT) and more recently SPECT/CT have been the workhorse modality for nuclear myocardial perfusion imaging (MPI). It is a widely available and validated non-invasive test to diagnose coronary artery disease, stratify risk, predict outcomes, guide patient management, and control costs (1-5). Positron emission tomography (PET) MPI has thus far been constrained to a limited number of centres, mostly due to the need for a cyclotron to produce the necessary short-lived radiotracers: N-13 ammonia ($^{13}\text{NH}_3$) and O-15 water (H_2^{15}O). Recently, the generator-based radio-

tracer Rubidium-82 (^{82}Rb) has been of increasing interest in the Netherlands as PET-based imaging, with its intrinsically preferable properties compared to SPECT in general and in the setting of MPI in particular, becomes attractive even in non-academic centres. ^{82}Rb has been in use as the standard MPI at the Jeroen Bosch Hospital since 2012 with an automatic-operating-generator constructed by dr. R.A.M.J. Claessens and in the Meander Medical Center since 2014 using the commercially available Bracco generator.

Tracer aspects

The rubidium-generator (figure 1) contains accelerator-produced strontium-82 (^{82}Sr) adsorbed on stannic oxide in a lead-shielded column and provides a means for obtaining solutions of ^{82}Rb in the chemical form of rubidium chloride ($^{82}\text{RbCl}$). ^{82}Sr decays to ^{82}Rb with a ^{82}Sr half-life of 25 days (600 hrs). The ^{82}Sr is produced in an accelerator by proton spallation of molybdenum, Mo (p, spall) ^{82}Sr or by the reaction ^{85}Rb (p, 4n) ^{82}Sr . The ^{82}Sr produced

has no carrier added. ^{82}Rb in turn decays by positron emission and associated gamma emission with a physical half-life of 75 seconds.

Compared to the other PET-tracers available, ^{82}Rb has a high-energy positron with considerably longer maximum and mean ranges before annihilation occurs (table 1). As spatial resolution degrades as the kinetic energy increases (6), ^{82}Rb has the lowest spatial resolution of the commonly available PET-tracers. Nevertheless, its spatial resolution still outperforms common SPECT imaging and this lower spatial resolution means that there is less of a learning curve when moving from SPECT MPI to ^{82}Rb PET MPI; compared to $^{13}\text{NH}_3$ images, where regional differences in myocardial thickness (especially near the apex) are more pronounced, ^{82}Rb images are "SPECT-like" in appearance (figure 2) but at a decidedly higher image quality (7,8).

Stress testing and acquisition

Due to the short half-life of ^{82}Rb and the need to image the influx-phase



Figure 1. Rubidium infusion system next to the PET camera in the Meander Medical Center.

Table 1. Properties of available PET MPI tracers.

pharmaceutical	isotope	half-life	production	physiology	positron range (mm in H ₂ O)	
					mean	max.
rubidium	⁸² Rb	76 seconds	generator	extracted/retained	5.9	17.0
water	¹⁵ O	122 seconds	cyclotron	freely diffusible	3.0	8.4
ammonia	¹³ N	10 minutes	cyclotron	diffusible/retained	1.8	5.5
acetate	¹¹ C	20 minutes	cyclotron	extracted/metabolized	1.2	4.2

from the blood pool into the myocardium for flow measurements, all aspects of ⁸²Rb PET MPI need to be performed inside the PET camera. As patients need to remain as motion-free as possible, ergometric stress testing is not feasible and patients are stressed through pharmacological means. The most common protocols employ either adenosine or regadenoson, both vasodilating agents. The largest advantage of adenosine is its low cost and the large body of experience using it as a pharmacological stressor. Downsides are the need for constant infusion during the stress test, necessitating two IV lines (one for adenosine, one for ⁸²Rb infusion) and side-effects, most notably advanced conduction blocks and hyperreactivity in asthma patients. Due to the short biological half-life of approximately ten seconds, such side-effects are usually self-limiting after cessation of adenosine administration.

Regadenoson is a selective A2A adenosine receptor agonist which elicits fewer side-effects and can be administered as a slow bolus, making it feasible to perform the stress test with only one IV line. Its greatest drawback is its cost, approximately fifty times that of adenosine. That cost is partially recovered through reduced costs for other materials and an increase in scan-time efficiency.

Acquisition

Acquisition protocols for ⁸²Rb MPI are outlined in figure 3. Using adenosine a stress-rest protocol can be used because of the shorter half-life of adenosine. With regadenoson, acquisition starts with the rest perfusion scan. In short, a topogram is acquired to ascertain the position of the heart, followed by a non-triggered low dose CT for attenuation correction. Rest perfusion images are acquired directly

after, over a period of seven minutes. Three minutes later, when the generator has generated sufficient ⁸²Rb and the rest activity has decayed sufficiently, the pharmacological stressor is administered and stress imaging begins. During these acquisitions the low dose CT can be checked for errors such as breathing artefacts, and if judged inadequate for attenuation correction a second CT can be acquired at the end of the protocol.

There is no stress-only protocol as the combined radiation dose of the stress and rest ⁸²Rb dose together is approximately 2.8 mSv, nearly half of the radiation dose of a stress-only ^{99m}Tc SPECT examination, and the entire stress-rest or rest-stress protocol can be performed within 45 minutes as opposed to common two-day protocols for SPECT MPI, with each visit taking up to three hours.

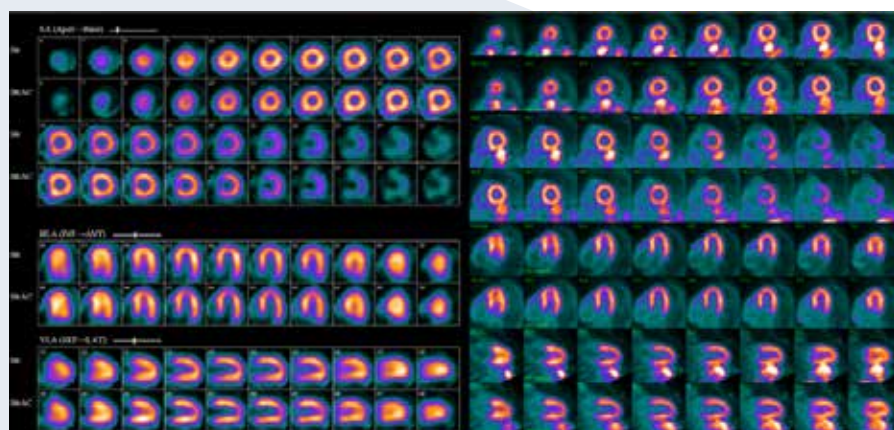


Figure 2. Comparison of stress-only ^{99m}Tc-tetrofosmin SPECT (without and with attenuation correction, left) and stress-rest ⁸²Rb PET MPI in the same patient. Although spatial resolution of the PET images is better, the images are essentially comparable.

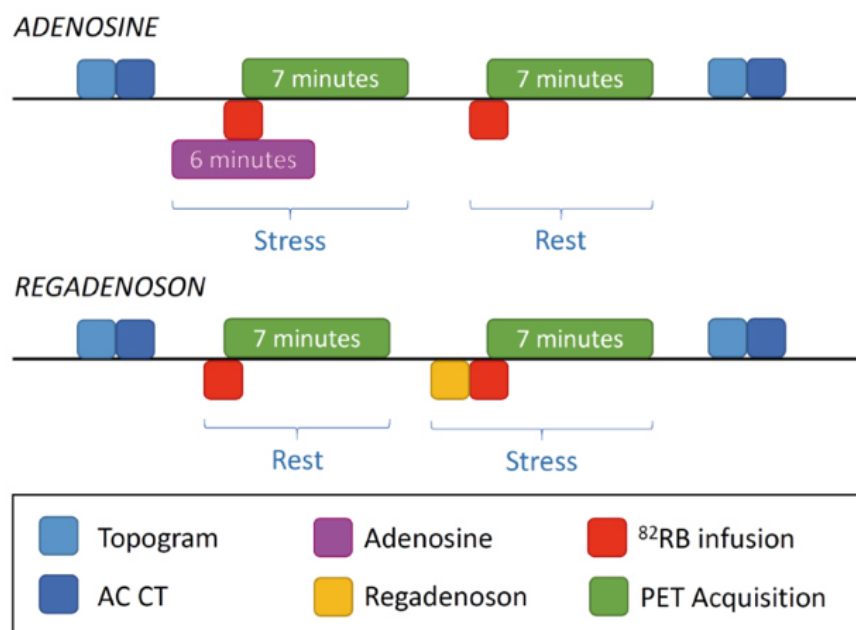


Figure 3. Acquisition protocols for ^{82}Rb PET MPI.

Reconstruction

7-minute list mode acquisitions of both the rest and the stress images are reconstructed into multiple subsets:

- A dynamic subset for flow quantification of the first five minutes, reconstructed as one 10 second frame, eight 5 second frames, three 10 second frames, two 20 second frames and three 60 second frames
- Static perfusion images containing the information from 2.5 - 7 minutes
- Gated images containing the information from 1.5 - 7 minutes

All images are attenuation corrected, with an additional non-corrected reconstruction of the static images.

Quantification of flow

The technical aspects of PET/CT perfusion quantification will be discussed in detail in the article by Van Dijk et al. elsewhere in this issue. Briefly, by measuring the input function at the level of the left ventricle lumen, measuring uptake into the myocardium and taking into account the single-compartment model for ^{82}Rb , blood flow at the level of the myocardium can be calculated in millilitres per gram per minute (mL/g/

min). Normal ^{82}Rb -values for rest flow are between 0.8 and 1.2 mL/g/min after correction for the rate pressure product, the product between the systolic blood pressure and heart rate, which should be normalised to 8000. During vasodilation, flow should increase to at least 2.0 mL/g/min, with coronary flow reserve (CFR, expressed as stress flow/rest flow) preferably above 2.5.

Clinical implementation

With greater image quality and robust flow quantification, the interpretability of ^{82}Rb PET MPI is superior to standard SPECT MPI. A meta-analysis by McArdle et al. (8) showed superior diagnostic accuracy for ^{82}Rb PET over $^{99\text{m}}\text{Tc}$ SPECT MPI. Even though contemporary, state-of-the-art SPECT studies with attenuation correction were included for the analysis and ^{82}Rb imaging did not include flow quantification, ^{82}Rb PET still outperformed $^{99\text{m}}\text{Tc}$ SPECT with a pooled sensitivity of 90% versus 85%, pooled specificity of 88% versus 85%, and an area under the summary receiver-operating characteristic curve of 0.95 versus 0.91. Although SPECT MPI performed better under these stringent inclusion criteria than in many

larger meta-analyses, it could not match ^{82}Rb PET.

Additionally, a meta-analysis by Jaarsma et al. which included SPECT, MRI and PET imaging for coronary artery disease concluded that PET as a modality had the highest accuracy and area under the curve (3).

As visual and semi-quantitative analyses (both for SPECT MPI and ^{82}Rb PET MPI) are based on the relative regional differences between areas of the left ventricle in a (stress or rest) scan, and differences in regional distribution between rest and stress images, they are prone to underdiagnose diffuse flow abnormalities as these are normalised in the scale. Through absolute quantification of flow, this confounding factor is neutralised. However, as measurements are performed on the level of the myocardium, it is not possible to differentiate multivessel epicardial disease which requires invasive treatment from microvascular disease that will not benefit from epicardial procedures. It seems justified that these patients receive coronary angiography to exclude significant epicardial coronary disease, at which point microvascular disease may be set

Table 2. Radiation dose for adults in cardiac nuclear imaging with technetium-compounds and rubidium.

tracer	half-life	procedure	effective dose ($\mu\text{Sv}/\text{MBq}$)	dose, MBq	effective dose, mSv
$^{99\text{m}}\text{Tc}$ -sestamibi	6 h	rest	9.0	700-900	6.3-8.1
		stress	7.9	700-900	5.5-7.1
$^{99\text{m}}\text{Tc}$ -tetrofosmin	6 h	rest	7.6	700-900	5.3-6.8
		stress	7.0	700-900	4.9-6.3
^{82}Rb	76 s	rest/stress	1.25	1100-1500	1.4-1.9

as the final diagnosis.

Quantitative perfusion analysis adds prognostic information, also in patients without perfusion abnormalities (9). Additionally, even if ischaemia is visible by visual and semi-quantitative means, flow measurements may show abnormalities in visually normal flow territories (figure 4), essentially “upgrading” patients from single vessel to multivessel disease with its concomitant adverse effect on prognosis (10). Parkash et al. reported larger defect sizes in 3-vessel disease with quantification ($69 \pm 24\%$) as opposed to relative analysis ($44 \pm 18\%$, $p=0.008$) (11).

Another advantage of PET MPI is that gated acquisition is performed at stress and rest. Although this is mostly a vasodilation stress, information of the contractile function both at peak stress and

in rest are obtained. This provides extra information in the same study.

Ziadi et al. demonstrated that ^{82}Rb -based CFR measurement was an independent predictor of 3-vessel disease which showed a higher diagnostic sensitivity for multivessel involvement (88%) than combined other risk factors such as reduced ejection fraction at peak stress, trans ischaemic dilatation and ECG changes (60%) (12).

When convenient, acquisition can easily be extended with a calcium score CT or even a coronary angio CT to provide even more information.

Radiation exposure

As mentioned earlier, ^{82}Rb PET has a lower radiation burden than common $^{99\text{m}}\text{Tc}$ SPECT imaging (table 2), although dose reduction in SPECT MPI is a field

in motion with lower possible doses reported through the use of dedicated camera types such as multi-pinhole cadmium zinc telluride camera systems. The entire rest-stress protocol performed with $2 \times 1110 \text{ MBq } ^{82}\text{Rb}$ and low dose CT for attenuation correction can be performed at a radiation dose of approximately $2.8 + 0.4 = 3.2 \text{ mSv}$ as opposed to doses upwards of 12-14 mSv for common comparable SPECT/CT protocols (5,13,14).

Additionally, as the maximum dose is delivered during the scan itself and dissipates quickly due to the short half-life of ^{82}Rb , the total dose per examination for the imaging technicians is also significantly reduced (15).

Future perspectives

The current gold standard for ob-

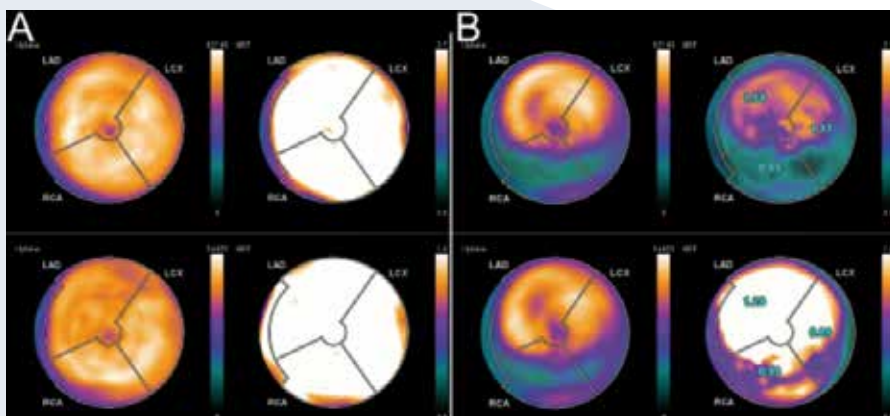


Figure 4. A: Normal perfusion on relative (left) and quantitative (right) bull's eye plots. B: Relative images indicate inferior wall infarction with minimal ischaemia, but quantitative analysis shows diffuse hypoperfusion of the entire left ventricle during stress, indicative of significant three vessel disease. Upper row: stress images, lower row: rest images.

structive coronary disease is invasively measured fractional flow reserve (FFR) which measures the decrease in pressure over a single stenotic lesion. As PET flow measurements are performed at the level of the myocardium, they take into account all flow reducing stenoses in the course of a coronary vessel. It is possible that consecutive lesions that, each on their own, only show moderate abnormalities on FFR may together produce a significant flow reduction at the level of the myocardium. Currently no conclusive data on this phenomenon exists but when flow measurements become more widely available further research regarding the relation between PET flow measurements and FFR measurements could and should be performed.

Conclusion

⁸²Rb PET MPI outperforms SPECT MPI in image quality, diagnostic accuracy and both time and radiation burden for the patient and personnel, without the need for a cyclotron on-site. It allows for quantitative measurement of myocardial blood flow, which has additional clinical value over visual and semi-quantitative analysis alone.

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References

1. International Atomic Energy Agency. Nuclear cardiology: Its role in cost effective care. Vienna: International Atomic Energy Agency; 2012
2. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107:2900-7
3. Jaarsma C, Leiner T, Bekkers SC, et al. Diagnostic performance of non-invasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: A meta-analysis. *J Am Coll Cardiol*. 2012;59:1719-28
4. Metz LD, Beattie M, Hom R, et al. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: A meta-analysis. *J Am Coll Cardiol*. 2007;49:227-37
5. Ghotbi AA, Kjaer A, Hasbak P. Review: Comparison of PET rubidium-82 with conventional SPECT myocardial perfusion imaging. *Clin Physiol Funct Imaging*. 2014;34:163-70
6. Beanlands RS, Youssef G. Diagnosis and prognosis of coronary artery disease: PET is superior to SPECT: Pro. *J Nucl Cardiol*. 2010;17:683-95
7. Bateman TM, Heller GV, McGhie AI, Friedman JD, Case JA, Bryngelson JR, et al. Diagnostic accuracy of rest/stress ECG-gated rb-82 myocardial perfusion PET: Comparison with ECG-gated tc-99m sestamibi SPECT. *J Nucl Cardiol*. 2006;13:24-33
8. Mc Ardle 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
9. Farhad H, Dunet V, Bachelard K, et al. Added prognostic value of myocardial blood flow quantitation in rubidium-82 positron emission tomography imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14:1203-10
10. Saraste A, Kajander S, Han C, Nesterov SV, Knuuti J. PET: Is myocardial flow quantification a clinical reality? *J Nucl Cardiol*. 2012;19:1044-59
11. Parkash R, deKemp RA, Ruddy TD, et al. Potential utility of rubidium 82 PET quantification in patients with 3-vessel coronary artery disease. *J Nucl Cardiol*. 2004;11:440-9
12. Ziadi MC, Dekemp RA, Williams K, et al. Does quantification of myocardial flow reserve using rubidium-82 positron emission tomography facilitate detection of multivessel coronary artery disease? *J Nucl Cardiol*. 2012;19:670-80
13. Senthamizhchelvan S, Bravo PE, Lodge MA, et al. Radiation dosimetry of ⁸²Rb in humans under pharmacologic stress. *J Nucl Med*. 2011;52:485-91
14. Di Carli MF, Murthy VL. Cardiac PET/CT for the evaluation of known or suspected coronary artery disease. *Radiographics*. 2011;31:1239-54
15. Tout D, Davidson G, Hurley C, et al. Comparison of occupational radiation exposure from myocardial perfusion imaging with Rb-82 PET and Tc-99m SPECT. *Nucl Med Commun*. 2014;35:1032-7