

REVIEW ARTICLE – DEBATE ARTICLE : WHICH PET FLOW TRACER IS THE BEST FOR MBF QUANTIFICATION?

⁸²Rb is the Best Flow Tracer for High-volume Sites

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Abstract

Rubidium-82 is the most well-established cardiac PET flow tracer with over 6 decades of literature. Due to its robust supply, short physical half-life, ease of use, low radiation dose and favorable kinetics it can deliver comprehensive clinical information with minimal risk and maximum convenience to patients and clinical staff. Optimized ⁸²Rb protocols can deliver high quality myocardial perfusion imaging, functional cardiac images and absolute myocardial blood flow and flow reserve from a single session 30 minutes clinical protocol—benefiting patient convenience and clinical throughput. In a high volume setting the cost of ⁸²Rb PET can be dramatically lower than that of alternative PET flow tracers. These factors compound toward ⁸²Rb as the best PET flow tracer for high-throughput clinics.

Keywords: Cardiac flow, Myocardial blood flow, Perfusion, Positron emission tomography, Rubidium-82 chloride

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Of the PET perfusion tracers currently available to clinicians, without a doubt Rubidium-82-chloride (⁸²Rb) is the most commonly used, especially in the United States and Canada. The popularity of ⁸²Rb is partly historical, as it has been recognized as a biological analog to potassium since 1953, and that its uptake is proportional to myocardial blood flow (MBF) was demonstrated as early as 1959. ⁸²Rb is the product of strontium-82 (⁸²Sr) decay and ⁸²Sr/⁸²Rb generators have been commercially available under the brand name CardioGen-82® (Bracco Imaging, Milano, Italy) since 1989 when USFDA approval was first granted. In 2016 Jubilant-DraXImage (Kirkland, Quebec, Canada) launched an alternative product under the name Ruby-Fill® which similarly comprises of a ⁸²Sr/⁸²Rb generator that is used with a specialized infusion system. At least one of these ⁸²Rb products is approved for clinical use in most developed countries including USA, Canada, EU, Japan, India, UAE, South Africa, Luxemburg, Switzerland.

Because of ⁸²Rb's long history and widespread adoption, a robust body of literature has been produced concerning its

characterization and clinical application. ⁸²Rb flow has been validated in large animals with surgically induced infarcts (1–3) and it has been demonstrated to have prognostic and diagnostic utility in numerous clinical trials both without and with the incremental value of quantitative myocardial blood flow (MBF) (4). MBF has been compared with invasive fractional flow reserve measurements demonstrating partially complimentary information from the two exams (5), which supports the use of ⁸²Rb as a gate keeper to the cath-lab or operating room in patients suspected of coronary artery disease (CAD) (6).

While other PET flow tracers with attractive properties have been developed, the use of ⁸²Rb has continued to grow year-after-year for few fundamental reasons. Many of the attributes of ⁸²Rb are derived from its short radioactive half-life of 76 seconds, its convenient generator-based productions, the robust and scalable ⁸²Sr supply chain, and the favorable kinetics of Rb as a cardiac perfusion agent (high uptake and long retention).

The goal of this article is to elaborate on the advantages of

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Table 1 Advantages of ^{82}Rb as a flow tracer

Low dose:
- Lowest radiation dosimetry of all flow tracers
- Exceedingly low occupational exposure to technologist staff due to fully automated injection
Robust supply:
- Multi-national generator manufacturers
- No expensive on-site cyclotron required
Patient convenience:
- Short, single session imaging protocol (<30 min for perfusion images, LVEF reserve, MBF reserve, Calcium, LV size)
Cost effective:
- Short, single session imaging protocol
- Most cost-effective for high throughput cardiac PET labs due to fixed generator costs
Well studied:
- First cardiac PET tracer approved by FDA
- First PET tracer approved for reimbursement in the US
- Approved in the most countries world-wide
- Highest number of clinical sites (>200 world-wide)
- Only tracer with studies of clinical value of LVEF reserve
- Largest studies of MPI prognostic value
High quality uptake images:
- High retention fraction which produces clinically interpretable MPI and LVEF.
- Detection of peak-stress (ischemic) wall motion abnormalities, as opposed to post-stress (stunned) defects.
- Short half-life does not require rest-stress delay or subtraction of rest-residual activity (^{18}F -or ^{11}C -based tracers).
- Extraction and retention fraction are higher than SPECT tracers, with retention most similar to ammonia at rest and stress.
- No lateral wall variant which reduces specificity for LCX disease (^{13}N -ammonia)
- No labelled metabolites in the blood which complicate tracer kinetics (^{13}N -ammonia)
- No lung uptake in congestive heart failure or smokers which makes PET-CTAC difficult (^{13}N -ammonia)
- No liver uptake which can interfere with RCA (^{13}N -ammonia)
Incremental clinical value of myocardial blood flow (MBF) and flow reserve (MFR) quantification:
- Highly reproducible MBF and MFR quantification
- Highest number of approved software programs (7 to-date)
- Multi-Software reproducibility is well established with consistent extraction curves
- Largest number of studies of MBF prognosis
- MBF validation studies in animals and humans
- Validation studies linked to FFR
- Only tracer with validated and reproducible measurements of same-day and separate-day test-retest repeatability (10% and 20% COV) which are equivalent or superior to ^{15}O -water
- Highest number of papers using coronary flow capacity to aid clinical interpretation and to guide revascularization decisions
- Does not require super-fast bolus injection for accurate measurement of stress flows (^{15}O -water)
- Ultra-simplified 2-frame acquisition can be used on 2D scanners.

^{82}Rb over alternative PET flow tracers. Key advantages are summarized in Table 1 and expanded upon in the text. To remain objective, limitations of ^{82}Rb are addressed along with possible solutions. The reader is expected to develop an understanding ^{82}Rb as an almost ideal tracer for routine myocardial perfusion imaging and myocardial blood flow quantification in clinics with large referral base.

Stable ^{82}Rb supply

^{82}Sr activity can be manufactured on demand by several technologies using particle accelerators as opposed to expensive and scarce nuclear reactors. Consequently, ^{82}Sr activity has historically been robust and can be relatively easily scaled up to meet growing market demands. ^{82}Sr has a sufficiently long physical half-life ($t_{1/2} = 25$ days) to enable shipping to remote destinations and affords tolerance to production and shipping delays of even several days. $^{82}\text{Sr}/^{82}\text{Rb}$ generator production currently exists in the US and Canada

and as demand continues to grow it is reasonable to expect industry to gradually increase the number of production facilities feeding the supply chain to both meet market demands and further enhance redundancy.

A generator reaches the end of its useful life when the amount of ^{82}Rb activity it can deliver falls below that required to achieve diagnostic image quality. Available ^{82}Rb activity follows the exponential decay of ^{82}Sr activity and therefore based on initial generator activity and clinically desired activity levels replacement can be forecast and scheduled well in advance. The old generator is replaced with a new one much like a printer ink cartridge, which can be performed by a trained nuclear medicine technologist without the need for radiochemistry staff. The typical life span of a generator ranges from 4 to 8 weeks depending on clinical needs and vendor specifications. Since many practices use patient weight-based dosing for PET imaging, one may extend the life of the generator by scheduling smaller patients to coincide

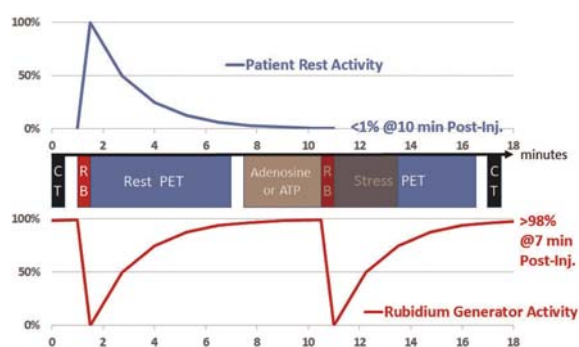


Figure 1 ^{82}Rb rest-stress imaging protocol is completed in under 20 minutes.

with the end of life of a generator and larger patients to the following week, when a new generator is installed.

The generator column contains a Ph-buffered tin-oxide resin matrix that, binds Sr ions but does not bind Rb. When the column is flushed with 0.9% NaCl saline the ^{82}Rb activity is washed off the column in the form of ^{82}Rb -chloride and Sr activity remains bound to the column (7). Because ^{82}Rb has a much shorter radio-active half-life than its parent, ^{82}Sr , the activity in the generator reaches secular equilibrium within several minutes as described by the Bateman equations (Red curve in Figure 1) (8). Within only 6 minutes of removing all the ^{82}Rb activity in the generator, roughly 96% of peak ^{82}Rb activity is replenished in the generator, and ~99% is replenished within 8 minutes. At this point the generator may be eluted again, enabling a clinic to perform a patient study every few minutes.

Activity administration must be performed using a direct infusion from the generator to the patient by intravenous (IV) injection, as the ^{82}Rb is too short-lived to assay a patient dose manually. Delivery is typically performed using an automated, dedicated elution system that monitors the activity eluted the generator in real-time and stops the elution when a target activity has been reached. Modern systems add advanced functions such as a saline push at the end of the elution to deliver all the activity to the patient and reduce outside scatter, finely controlled activity delivery profiles, record keeping and robust quality control (9).

Low radiation dose

Table 2 compares dose per unit of activity for the most common PET flow tracers along with typical administered activity and resulting effective dose associated with a combined rest-stress exam. As can be seen, the radiation dose to patients is exceptionally low with ^{82}Rb , mostly due to the extremely short radio-active half-life. Furthermore, because rest and stress imaging can be performed in a single imaging session, a single, low-dose CT can be used for attenuation correction of both images, further reducing radiation dose

compared to longer lived tracers requiring separate imaging sessions and two CTs. A complete ^{82}Rb PET rest-stress scan can be achieved with effective dose <2 mSv including a low-dose CTAC (~0.25 mSv) (10, 11).

Likewise, radiation exposure to medical staff (technologists and nurses) is also low due to the short half- life of ^{82}Rb activity and automated activity delivery by the infuser which enables the technologist to exit the imaging room during activity administration (9).

The largest risk with ^{82}Rb is inadvertent administration of ^{82}Sr activity to the patient via premature strontium breakthrough from the column or mistaken use of a solution other than 0.9% NaCl saline which could decondition the column. To mitigate this risk, modern elution systems automatically enforce a stringent quality assurance protocol that includes testing of the generator eluate each day before enabling its clinical use (9). Daily quality control can be performed by a trained nuclear medicine technologist with the infuser provider quality assurance oversight to mitigate user errors.

Short imaging times

Roughly 2 minutes after ^{82}Rb administration, much of the activity distributes into the heart where it is retained and by 8 minutes (>6 half-lives) almost all the activity has decayed. Hence image acquisition begins immediately following Rb administration and lasts less than 8 minutes. Figure 1 illustrates a typical image acquisition protocol using ^{82}Rb PET starting with a scout scan for patient positioning, CT for attenuation correction (CTAC), ^{82}Rb administration and rest image acquisition, pharmacologic stress and a second ^{82}Rb administration and a stress image acquisition. By the time that pharmacologic stress is achieved, and stress imaging can begin, no residual rest activity remains (blue curve in Figure 1) and hence the two scans can be performed in a single session without removing the patient from the scanner bed and without cross-talk interference between the rest and stress scans (such as with ^{18}F , ^{11}C and ^{13}N based tracers). Consequently, a single CTAC can be used for both rest and stress scans—reducing radiation dose, increasing clinical throughput and improving patient convenience.

The entire rest-stress imaging protocol can be completed within 30 minutes with able-bodied patients and in less than 45 minutes even in patient with severe mobility constraints. These short imaging times are better tolerated by many patient populations including those with arthritis, congestive pulmonary diseases (e.g. sleep apnea) and obesity. Furthermore, short imaging times help reduce image artifact associated with patient motion.

The protocol depicted in Figure 1 images the patient at peak-stress wall motion abnormalities associated with ischemia, compared to post-stress imaging studies that visualize

Table 2 Properties of common PET blood flow tracers (12)

Tracer	Physical half-life (min)	Mean positron range (mm)	Production Method	Injected activity* (MBq)	Effective Dose Constant (mSv/GBq)	Rest+Stress Effective Dose (mSv)	Comments
⁸² Rb-chloride	1.27	2.60	Generator (⁸² Sr) eluate	1000	0.8 (10)	1.6	Reasonable uptake-to-flow relation Requires direct injection system Suitable for rapid serial imaging
¹³ N-ammonia	10.0	0.57	Cyclotron purified	500	2.7 (13)	2.7	Excellent uptake-to-flow relation Lateral wall defect normal variant Variable liver and lung uptake
¹⁵ O-water	2.05	1.02	Cyclotron purified	1110	0.9 (13)	2.0	Requires direct injection system Ideal washout-to-flow relationship MPI not possible
¹⁸ F-Flurpiridaz	109.8	0.23	Cyclotron synthesized	140 rest 320 stress	19 (14)	8.7	Excellent uptake-to-flow relation Currently in Phase-3 trials

Legend: *=Approximate with 3D PET

myocardial stunning, which is less sensitive to early disease (15). While exercise stress (treadmill or bicycle) have been demonstrated to be feasible with ⁸²Rb (16), these are difficult to perform and not recommended for patients that struggle to move briskly in a safe manner. Exercise stress may also cause excessive respiratory and body motion that could adversely impact image quality.

Using list-mode PET acquisitions starting immediately with tracer administration various image sets can be reconstructed for comprehensive clinical interpretation, including static, respiratory-gated and cardiac-gated uptake phase images (each at rest and stress states). The same acquisitions can also be used to generate dynamic image sequences of the tracer distribution process which can subsequently be processed to measure myocardial blood flow in absolute units of mL/min/g.

Myocardial perfusion imaging and cardiac function

PET offers accurate attenuation correction, higher count statistics and better spatial resolution than SPECT. Thus, in comparison to SPECT, ⁸²Rb MPI is interpreted with greater overall confidence, very few tests are equivocal (17), and diagnostic accuracy is higher (18). Rb extraction by the myocardium is higher than all currently available SPECT tracers (4) and once it is taken up by the myocardium it is retained longer. Rb uptake images possess high myocardium to background contrast without the need for complex image analysis—a significant limitation of ¹⁵O-water, which is not retained in the myocardium and requires complicated processing of dynamic image sequences to generate uptake images. Despite ⁸²Rb first-pass extraction being lower than that of other PET flow tracers, it is retained in the myocardium (independently of ischemic state) longer than ¹³N-ammonia or ¹⁵O-water, resulting in a net uptake on the same order of that of ¹³N-ammonia and producing similar quality myocardium to background contrast (4).

Compared to most neighboring structures including the blood, lungs, liver and spleen, myocardial activity is high and rarely suffers from neighboring interference from other organs (17). With ¹³N-ammonia, for example high liver uptake is common and frequently interferes with interpretation of the inferior wall region, high lung uptake can also be present in congestive heart failure, chronic pulmonary disease or smokers (19). Nevertheless, ⁸²Rb stomach uptake has been documented and can interfere with interpretation of the inferior wall in a small subset of patients (17). A study by Orton et al. (20). demonstrated stomach spill-in interference in 18% and 8% of rest and stress scans respectively. Stomach interference, however, can be reduced by instructing the patient to consume 1–2 cups of water prior to imaging, which may reposition or distend the stomach wall (21). If stomach uptake is noticed on rest imaging, the protocol may be interrupted and resumed later after the patient has eaten and/or drank. With newer, higher resolution PET, optimal patient management and expert image interpretation stomach uptake rarely results a non-diagnostic test.

Static uptake and cardiac gated images can be readily reconstructed from the list-mode data, enabling contemporary myocardial perfusion image (MPI) interpretation using the data after –2 min post-administration. By this time high myocardium to blood contrast can be observed due to rapid clearance of Rb from the blood plasma, low binding to red blood cells and lack of Rb labelled metabolites [contrary to ¹³N-ammonia (12, 22)]. Furthermore, there is no potential for cross-talk interference between rest and stress images due to the rapid decay between scans (>8 half-lives) (contrary to ¹³N- and ¹⁸F-based tracers).

Another key advantage of ⁸²Rb is the very uniform normal uptake distribution with only minor and characteristic infero-apical reduction due to partial-volume effect at the LV apex. In contrast, ¹³N-ammonia has variable lateral wall uptake

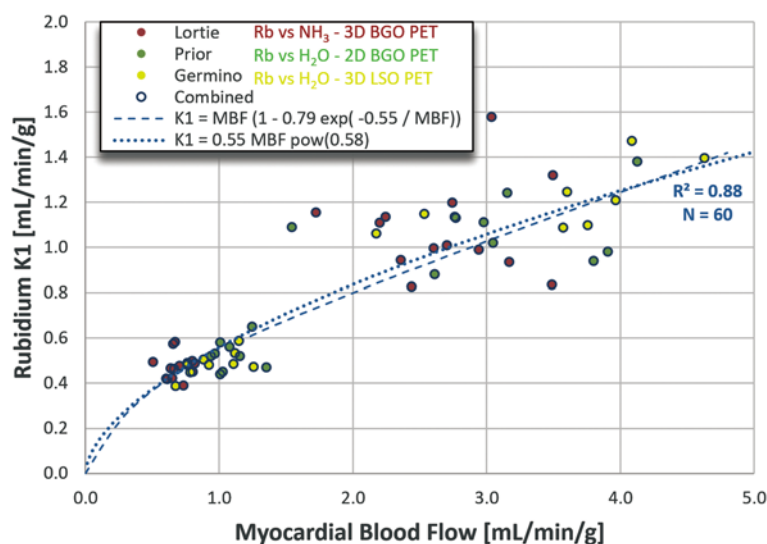


Figure 2 ^{82}Rb uptake rate ($K1 = \text{MBF} \times \text{Extraction}$) as a function of MBF.

patterns which can reduce specificity to detect disease associated with the left circumflex coronary artery (22, 23).

Cardiac-gating enables visualization cardiac wall motion and quantitative analysis of LV ejection fraction (LVEF), which improves specificity of MPI (4, 24). Further incremental value of LVEF reserve (stress-rest LVEF) is added specificity through for assessment of vasodilation response (>5% change) (25) and exclusion of 3-vessel CAD (26). Dorbala et al. demonstrated that LVEF reserve from ^{82}Rb PET MPI has incremental value to prognosticate adverse events in the largest study of its type to date (1432 patients) (27).

Imaging guidelines already recognize the comprehensive information available from the uptake phase images of ^{82}Rb PET including perfusion distribution patterns at rest and stress, LV function (including LV ejection fraction and wall motion) and LV size (4, 24). With improvements in PET imaging technology, there is a growing interest in expanding indications to right ventricle function (28). Furthermore, the low-dose CT for attenuation correction (CTAC) can provide sufficient information for accurate calcium scoring (29). By expanding image acquisition to include dynamic imaging, quantitative measurements of blood flow are also possible with no additional imaging time, radiation exposure or costs (30).

Quantification of myocardial blood flow with dynamic PET

With dynamic imaging, the introduction of ^{82}Rb activity to the venous blood stream and subsequent distribution to perfused tissues can be achieved including extraction of ^{82}Rb from blood to the myocardium. This extraction process can be modeled using a simple and robust 1-tissue-compartment kinetic model (30, 31). The rate of tissue uptake (K_1) must be corrected for flow dependent extraction fraction to derive

measurements of myocardial blood flow (MBF) (32). The ^{82}Rb uptake rate ($\text{MBF} \times \text{extraction}$) is shown as a function of MBF in Figure 2, as measured in 3 separate human validation studies using 2D and 3D PET imaging with ^{13}N -ammonia and ^{15}O -water as the gold-standards (32–34).

Measurement of MBF and MFR requires the use of dedicated image analysis software of which multiple software solutions have been developed (41) and validated to reproduce the same MBF values (42–44). Because these software are highly automated and the myocardium can be clearly delineated on ^{82}Rb uptake images they are nearly operator independent (45). The ratio between stress and rest MBF values is termed the myocardial flow reserve (MFR). A large body of literature exists on the topics of ^{82}Rb PET MBF and MFR as incremental prognostic (35–37) and diagnostic (38–40) value over relative perfusion imaging alone (4). An example Rubidium scan is shown in Figure 3 demonstrating the high quality of relative perfusion images, and the incremental value of flow quantification this patient with multi-vessel disease.

Rigorous studies of short-term reproducibility of ^{82}Rb MBF have been performed to determine optimal tracer administration protocol (46), dynamic image time frame sampling (47), image reconstruction (48), kinetic model (49) and extraction correction (both in 2D and 3D PET) (50, 51). Consequently the accuracy and precision of ^{82}Rb are well documented to be at the cutting edge of PET flow tracers (52), two fold better than those of SPECT (53, 54) and on par with those from ^{15}O -water (55). Short-term and multi-day reproducibility have corresponding coefficient of variations (COV) of ~10% and 20% respectively (46, 48, 56).

Reproducible ^{82}Rb infusion profiles have been demonstrated to produce more reproducible and precise absolute MBF measurements (46), but these infusion do not necessarily need

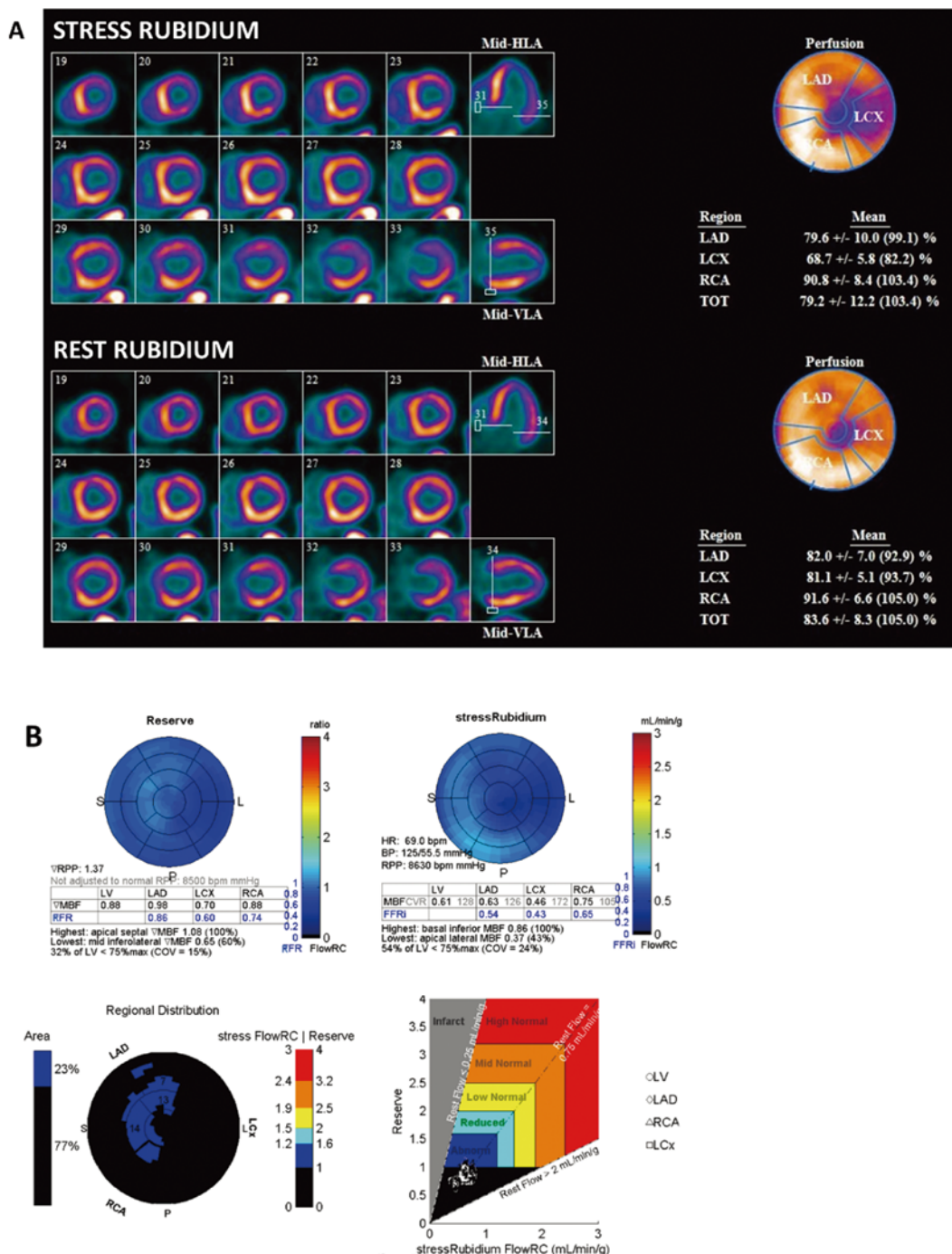


Figure 3 Rubidium PET study in 76-year-old man (118 kg, 180 cm, BMI 36.4) referred for assessment of chest pain. (A) Relative perfusion images suggested single-vessel disease in the left circumflex territory, with TID=1.2 also indicating the possibility of multi-vessel disease. (B) Flow quantification results demonstrate severe reduction in peak stress flow (0.61 mL/min/g and Flow Reserve (0.88) indicating myocardial steal in all three vascular territories (77% of the LV polar-map area). The patient was referred for invasive coronary angiography and was confirmed to have balanced 3-vessel disease.

to have a fast bolus shape as with ^{15}O -water PET. In fact, a small canine study demonstrated that MBF values were reproducible with ^{82}Rb infusions ranging from 15 to 240 seconds in length (30). Longer infusions resulted in lower camera peak count-rates, fewer dead-time losses, higher uptake phase counts, less image noise and more regionally-uniform uptake values. Slow infusions may therefore enable routine MBF quantification on older PET systems with limited

count rate capabilities (57). Because the kinetic properties of ^{82}Rb are so simple and robust even an ultra-simplified, 2 phase imaging protocol comprised of an integral blood activity phase and uptake phase has been shown to produce reasonably accurate blood flow measurements on 2D PET systems (58), so long as the infusion profile is reproducible (46).

Automated infusion system

The fast decay of ^{82}Rb necessitates infusion of ^{82}Rb activity

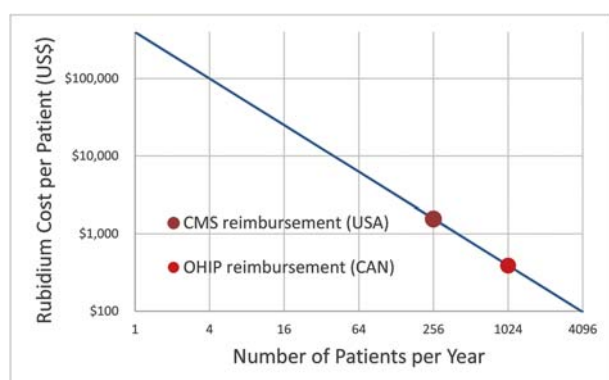


Figure 4 Per patient cost of ^{82}Rb as a function of clinical volume. Dots represent estimated break-even clinical volumes for different reimbursement jurisdictions. CMS is Centers for Medicare & Medicaid Services, OHIP is Ontario Health Insurance Plan.

from the generator directly to the patient via an intravenous (IV) line. Modern ^{82}Rb infusion systems precisely control the activity delivered to the patient including total activity (e.g. weight based), time duration and bolus shape (59).

The infuser is positioned near the PET/CT system and negates the need for clinical staff to manually draw doses in a hot-lab and transport them to the imaging suite. This improvement decreases physical strain on technologists, reduces the chance for workplace accidents and can increase clinical throughput. Automated infusion systems are also able to perform real-time quality control and to document the actual activity delivered to the patient.

Decreasing cost with clinical volumes

A fundamental difference of ^{82}Rb flow imaging compared to other tracers is that the tracer cost is fixed and independent of patient volumes. Thus, the larger the clinical volume, the lower the per-patient cost becomes as is demonstrated in Figure 4. In a high throughput clinical setting the ^{82}Rb tracer cost can compete with those of SPECT and easily beat out other PET tracers. Based on an assumed generator supply contract of \$400,000 per year, for a site imaging 2000 patients/year (~8 patients/day in 4 hours/day), total tracer costs (rest and stress) are less than \$200 per patient. A cardiac dedicated site performing 16 patients in an 8-hour workday can reduce its tracer costs to \$100 per patient. Under current reimbursement rates, ^{82}Rb PET can be economically favorable in high volume clinics.

^{82}Rb PET MPI has already been demonstrated to reduce downstream healthcare costs compared to SPECT by more appropriately filtering patients that may benefit from coronary arteriography or coronary artery bypass grafting (6). Although it has not yet been definitively demonstrated, one can reasonably assume that the comprehensive clinical information from rest-stress ^{82}Rb PET with MBF quantification further reduces adverse events due to appropriate treatment guidance

(60–62), further improving the return on investment for ^{82}Rb .

Limitations of ^{82}Rb

^{82}Rb does have several disadvantages that are worth noting. Firstly, the positron range of ^{82}Rb is significantly larger than that of ^{13}N and ^{18}F (see Table 2), which could limit image spatial resolution as clinical PET scanner technology improves to achieve <3 mm intrinsic spatial resolution. However, more significantly, because of the rapid ^{82}Rb decay, late uptake images are relatively count-poor so more smoothing is required to compensate for image noise which is the main factor driving image resolution. More sensitive PET systems, with longer axial bore size may help in this respect.

Because ^{82}Rb decays several half-lives over the course of a single acquisition, the PET scanner must operate over several count-rate orders of magnitude. On low count-rate capable PET scanners ^{82}Rb administration must be optimized to achieve accurate dynamic imaging and high-count uptake images within a single acquisition. Consultation with an expert imaging physicist is recommended to achieve optimal performance (57).

While the low extraction of Rb is often quoted as a limitation, sufficient clinical data exists to support the claims of ^{82}Rb as high-quality alternative for MPI and MBF for robust and comprehensive clinical decision making.

Conclusion

Rubidium-82 is an easy to use, low-dose tracer that provides comprehensive clinical information. Combined with the advantages of PET over SPECT imaging, and only minor drawbacks in comparison to alternative flow tracers ^{82}Rb PET imaging is ideal for high throughput clinical application.

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Conflicts of interests

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