Review

Generator-produced rubidium-82 positron emission tomography myocardial perfusion imaging—From basic aspects to clinical applications

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KEYWORDS
Generator; Myocardial blood flow; Positron emission tomography; Rubidium

Summary Cardiovascular disease is the leading cause of death in modern industrialized countries with an aging population. This fact has fueled the need for innovative diagnostic testing intended to improve coronary artery disease (CAD) patient care. Detection of myocardial ischemia using myocardial perfusion imaging (MPI) plays an important role for CAD diagnosis and the prediction of future risk of cardiovascular events. Positron emission tomography (PET) MPI has high diagnostic accuracy and can estimate regional myocardial blood flow (MBF) in patients with CAD. Rubidium-82 (\textsuperscript{82}Rb) is a generator-produced PET myocardial perfusion tracer and has been widely used in North America in clinical practice. \textsuperscript{82}Rb PET has recently become available in some cardiovascular centers in Europe and Japan. Clinical trials are expected in both regions. \textsuperscript{82}Rb PET has high diagnostic accuracy and recent data have shown its prognostic value. Thus, \textsuperscript{82}Rb PET would greatly contribute to CAD patients’ care. \textsuperscript{82}Rb PET can also be used to quantify MBF.

This review describes the current status of \textsuperscript{82}Rb MPI from basic principles to clinical implications. This paper also highlights the recent development of MBF quantification using \textsuperscript{82}Rb PET.

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Introduction

Coronary artery disease (CAD) continues to be a major cause of death both in modern industrialized countries and in developing countries. However, recent developments of coronary risk interventions have significantly reduced the risk of cardiovascular events. Thus, it is desirable to develop accurate and widely available noninvasive diagnostic testing to detect high-risk patients (vulnerable patients) [1].

The role of any diagnostic imaging test is to enhance the physician’s decision-making process so as to improve symptoms and outcomes in patients with CAD. Techniques for evaluating myocardial perfusion are important for identifying patients with CAD and for predicting their future cardiovascular events. Thus, physiological information greatly contributes to strategy management in patients with CAD and subjects with various coronary risk factors.

The increasing numbers of patients with CAD necessitate the development of simple and widely available diagnostic techniques. Positron emission tomography (PET) represents an advanced nuclear imaging technology using molecular probes to understand the physiological process [2]. In the past, clinical use of cardiac PET has been limited by the requirement for an expensive, on-site cyclotron for radioisotope production as well as expensive PET scanners. However, the development of less expensive PET/computed tomography (PET/CT) cameras and the increased use of PET for oncology imaging have resulted in a wider clinical application of cardiac PET. More than 1000 PET and PET/CT scanners have been installed in North America [3], and currently there are nearly 200 PET centers in Japan. Rubidium-82 (82Rb) is a PET myocardial perfusion tracer that is produced with a strontium-82 (82Sr)/82Rb generator and is widely used for the diagnosis of CAD in centers without immediate access to an on-site cyclotron [3,4]. Therefore, 82Rb perfusion studies could be applied in larger populations [5,6].

The US Food and Drug Administration (FDA) approved 82Rb generators for clinical use in 1989. US Medicare reimbursement began in 1995 [7] and is now approximately $1500 per rest-stress study. We estimate that there are currently about 120 sites where 82Sr/82Rb generators are in use in the USA. In Canada, The Ottawa Heart Institute manufactured a 82Rb generator in 1999 and Health Canada approved its investigational use in 2003. In response to the shortage of Technetium-99m (99mTc) in 2009, the ARMI (Alternative Radiopharmaceuticals for Medical Imaging) trial will support implementation of 82Rb PET in 10 new centers across Canada in 2010. To the best of our knowledge, the first 82Rb human study published outside of North America was published in Japan by Manabe et al. [8]. Recently, some cardiovascular centers in Europe and Japan have initiated 82Rb studies [8,9]. Thus, 82Rb could be available worldwide in the near future.

Measurement of regional myocardial blood flow (MBF) permits the evaluation both of the physiological significance of coronary lesions and of vascular function in subjects with coronary risk factors [2,10]. PET MBF quantification is conducted mainly using 15O-labeled water and 13N-ammonia [2,10—12]; however, 82Rb can also be used to estimate regional MBF using appropriate mathematical models [8,13—15].

82Rb tracer characteristics

Rubidium has been studied in the context of myocardial perfusion since the late 1950s [16]. Rubidium is rapidly extracted from the blood and is taken up by the myocardium in relation to myocardial perfusion, which requires energy for myocardial uptake through Na/K-ATPase similar to thallium-201 [17]. Most recently introduced rubidium-82 (82Rb) can generate a clear perfusion image, similar to conventional single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) because 82Rb is an extractable tracer. Cell membrane disruption may cause rapid washout of 82Rb from the tissue and 82Rb can identify viable myocardium [18]. In animal models, the first-pass extraction fraction is 50–60% at rest and uptake decreases with increased flow (Fig. 1) [19—21].
Among PET perfusion tracers, $^{82}$Rb has the shortest physical half-life with 76 s (Table 1) [2,10]. The short physical half-life makes $^{82}$Rb suitable for repeated and sequential perfusion studies, which usually require 10-min intervals (Fig. 2) [8,14]. The short half-life requires rapid image acquisition shortly after tracer administration, which can reduce a total study time. Because of its short half-life, $^{82}$Rb presents limited radiation exposure for patients (5.5 mSv for 60 mCi) [22]. Thus, a stress and rest $^{82}$Rb study has 11.0 mSv of total body radiation exposure. By comparison, a 1-day $^{99m}$Tc rest-stress study (10 mCi + 30 mCi) has 10.6–12.0 mSv radiation exposure and a thallium-201 stress-rest study (3 mCi) has 18.8 mSv of radiation exposure. Average USA background radiation exposure is 3.0 mSv/year [22].

The relatively high positron energy of $^{82}$Rb of 3.15 MeV is associated with a 2.60 mm RMS positron range and results in lower spatial resolution than is seen with $^{13}$N-ammonia with a 0.57 mm RMS positron range [23].

$^{82}$Rb generator and infusion system

As stated earlier, $^{82}$Rb is produced from a $^{82}$Sr/$^{82}$Rb (parent/daughter) generator which can be eluted every 10 min [24].

The generator encases an ion-exchange column (Fig. 3A) of tin oxide that binds with the parent isotope, $^{82}$Sr, but has low binding affinity for $^{82}$Rb. Flushing the generator with 0.9% NaCl solution elutes the $^{82}$Rb activity while the Sr remains bound to the column. Daily quality control includes $^{82}$Sr and $^{85}$Sr breakthrough measurements using a dose calibrator and pyrogen tests of the eluate. $^{82}$Sr and $^{85}$Sr breakthrough is based on the ratio of the eluate activity after sufficient time for $^{82}$Rb decay and the eluate activity immediately after the infusion is complete. It is important to measure $^{82}$Sr and $^{85}$Sr breakthrough because they have biochemical affinity to bone and could result in irradiation of the radio-sensitive bone marrow. Current radioisotope providers guarantee the quality of the generators for 4–8 weeks, at which point the available $^{82}$Rb activity is insufficient for clinical use.

The major expense associated with $^{82}$Sr/$^{82}$Rb generators is the cost of $^{82}$Sr. However, if the generator is utilized in a high throughput clinic, this cost can be offset. Others have demonstrated routine use of $^{82}$Rb PET for MPI at a cost similar to that for $^{99m}$Tc SPECT [25].

Due to the short half-life of $^{82}$Rb and the decreasing amount of available $^{82}$Rb as the generator ages, it is necessary to use an automated infusion system to administer the $^{82}$Rb eluted from the $^{85}$Sr/$^{82}$Rb generator directory to patients (Fig. 3B) [26]. A small and mobile infusion system is used for eluting $^{82}$Rb as often as every 10 min with low radiation exposure to medical personnel and patients [24].

Klein et al. have developed an automatic infusion system which produces accurate and reproducible constant-activity elution profiles of $^{82}$Rb activity, independent of parent $^{82}$Sr activity in the generator (Fig. 3A and B) [26,27].

Table 1: Common myocardial blood flow tracers.

<table>
<thead>
<tr>
<th>Tracer</th>
<th>PET/SPECT</th>
<th>Half-life</th>
<th>Scan time (min)</th>
<th>Positron energy (MeV)</th>
<th>Radiation dosage (mSv)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{82}$Rb</td>
<td>PET</td>
<td>76 s</td>
<td>6–10</td>
<td>3.15</td>
<td>16 (90 mCi)</td>
</tr>
<tr>
<td>$^{15}$O-water</td>
<td>PET</td>
<td>110 s</td>
<td>6–10</td>
<td>1.72</td>
<td>2.5 (60 mCi)</td>
</tr>
<tr>
<td>$^{13}$N-ammonia</td>
<td>PET</td>
<td>9.97 min</td>
<td>2–4</td>
<td>1.19</td>
<td>2.4 (30 mCi)</td>
</tr>
<tr>
<td>$^{99m}$Tc sestamibi/tetrofosmin</td>
<td>SPECT</td>
<td>6 h</td>
<td>12–15 (dual head camera)</td>
<td>–</td>
<td>12/10.6 (40 mCi)</td>
</tr>
<tr>
<td>Thallium-201</td>
<td>SPECT</td>
<td>72.9 h</td>
<td>12–15 (dual head camera)</td>
<td>–</td>
<td>25.1 (4 mCi)</td>
</tr>
</tbody>
</table>

*a Radiation dose is based on the total dose of standard rest/stress perfusion study and according to the data by Thompson and Cullom [22]. PET, positron emission tomography; SPECT, single photon emission computed tomography.
**82Rb PET perfusion image acquisition and processing**

Although some have reported on exercise tests with 82Rb, because of the short tracer half-life, stress perfusion imaging is usually performed by vasodilator pharmacological stress [3].

For accurate MBF quantification, 82Rb should be administered in such a manner that sufficient activity is present during the uptake phase but the camera is not saturated during the injection phase of the scan. This can be achieved by customizing the injected dose to the size of the patient and by performing infusion over 30 s or longer, rather than using a fast bolus. In 2D data acquisition, approximately 20 MBq/kg of 82Rb can be administered intravenously over 30–60 s followed by a serial dynamic acquisition using a PET camera with a high-count rate and high sensitivity [3,6]. Modern cameras without septa and with 3D data acquisition are more sensitive and therefore 10 MBq/kg can be used. A generator can be used as long as it passes daily quality assessment and has sufficient activity; thus, 3D imaging can double the useful life of each generator [10].

Static images acquired for 3–8 min and starting 70–150 s after completion of tracer injection can be used for MPI [3,6]. Scanners with list mode and electrocardiogram (ECG)-gating capabilities can use the same acquisition to generate static uptake images for MPI, dynamic image sequences for MBF quantification, and gated images for the evaluation of left ventricular (LV) function [28]. PET/CT hybrid systems are able to acquire CT images for attenuation correction in a fraction of the time required by PET cameras with transmission sources (Fig. 2) [7]. The total rest/stress data acquisition with a modern PET/CT can be as short as 40 min (Fig. 2). Thus, it may be possible to perform 10–12 rest/stress studies per day with a dedicated camera and sufficient staffing [28].

**Image processing and common artifacts**

Transaxial static images are typically reconstructed using filtered back projection, but iterative reconstruction methods are becoming more common with the introduction of more powerful computers. Iterative reconstruction algorithms can offer images with more favorable noise properties, better myocardium to blood pool contrast, and higher spatial resolution. Alternatively, iterative reconstruction may offer high quality images with a lower 82Rb dose, which would further decrease the patient dose.

One of the advantages of PET over SPECT is that with proper attenuation correction, PET provides reliable images, particularly in large patients, patients with large breasts, and with arms present in the field of view (FOV). 82Rb images sometimes have excessive bowel radioactivity, which can make interpretation of the inferior region difficult. This can often be detected with a quick reconstruction of the rest uptake frame while the patient is still on the bed, and can be resolved by instructing the patient to eat or drink water before repeating the image acquisition.

**Clinical applications with relative perfusion imaging**

**Diagnosis in coronary artery disease**

Standard visual perfusion imaging assessment is based on defining regional uptake relative to the maximum uptake in the myocardium. Regions with reduced uptake (so-called...
defects) represent functionally significant CAD (Fig. 4). This approach is applied for PET as well as SPECT MPI.

Recently, the Canadian Cardiovascular Society and colleagues conducted a systematic literature review for $^{82}$Rb and $^{13}$N-ammonia PET MPI in CAD diagnosis. The mean sensitivity and specificity of PET MPI are 89% and 89% with ranges from 83% to 100% and 73% to 100% in 14 studies including a total of 1460 patients [4]. Among the 14 studies, 6 studies evaluated the CAD diagnostic accuracy by $^{82}$Rb. To date, a total of 9 studies, with a total of 1151 patients, evaluated the diagnostic accuracy. The sensitivity and specificity are similar to the previous systematic review with 87.7% and 88.7% [29–37] (Table 2). Three recent studies used hybrid PET/CT scanners and showed similar sensitivity of 87.8%, and higher specificity of 95.7% [29,30,34]. Newer imaging crystals (e.g., LSO and BGO) can obtain higher count rates accompanied by the new generations of electronics. This may contribute to improved diagnostic accuracy using PET, by providing more counts for better image quality. Sampson et al. evaluated diagnostic accuracy of CAD using a PET/CT scanner. The sensitivity, specificity, and accuracy were 92%, 83%, and 87%, respectively. The diagnostic accuracy of $^{82}$Rb with PET/CT was also high in obese patients and women, who usually have poor image quality in most of the diagnostic imaging [34]. $^{82}$Rb PET may play an important role for these challenging populations.

Three studies have compared the diagnostic accuracy for detecting CAD with PET stress perfusion imaging and conventional SPECT stress perfusion imaging in the same patient population. The first two studies, which compared $^{82}$Rb PET with thallium-201 SPECT, included a greater number of patients with suspected CAD and showed higher sensitivity and specificity of PET perfusion imaging [31,36]. Today, $^{99m}$Tc SPECT MPI has largely replaced thallium-201 SPECT in many North American facilities because $^{99m}$Tc SPECT MPI has better image quality than thallium-201 due to its higher photon
Figure 4  Representative images from normal subject and 47-year-old man with coronary artery disease (CAD). (A) Normal subject: the $^{82}$Rb positron emission tomography (PET) images show normal perfusion at stress and rest. The attenuation correction contributes good image quality without any tissue attenuation artifact. (B) CAD patient with 99% stenosis in left anterior descending artery (LAD)\#6: $^{82}$Rb PET images show reversible perfusion defect in anterior, indicating myocardial ischemia in LAD territory.

energy and more widely administered activities. Important data from Bateman et al. evaluated the diagnostic accuracy of ECG-gated $^{82}$Rb PET MPI compared with ECG-gated 99mTc sestamibi SPECT in 112 studies. Using a 50% threshold of epicardial coronary artery stenosis, the diagnostic accuracy was higher in $^{82}$Rb PET than in SPECT ($p = 0.002$) [29]. Overall, the accuracy for the detection of coronary artery disease from pooled data derived from these 3 studies with 395 patients was greater for $^{82}$Rb PET than for SPECT with greater sensitivity of 98% versus 80%, specificity of 89% versus 65%, and diagnostic accuracy of 89% versus 77%.

PET MPI has several advantages over the conventional SPECT MPI. (a) The higher sensitivity of PET cameras means more photons are obtained from the myocardium, and higher quality myocardial images are provided. (b) Accurate correction of photon attenuation can be performed with PET. This contributes to reducing attenuation artifact. (c) $^{82}$Rb has relatively high extraction fractions which may permit detection of mild degrees of ischemia. These advantages of $^{82}$Rb PET may be particularly important for the comparison of perfusion imaging with PET versus SPECT using technetium-99m perfusion agents that have lower extraction fraction than does thallium-201. (d) Stress perfusion abnormalities can be identified with conventional SPECT in the majority cases; however, the interpretation of PET perfusion images is less equivocal, possibly due to the better quality images [29].

It is difficult to detect multivessel CAD using relative MPI. Transient ischemic dilatation (TID) is considered to be a marker of extensive myocardial ischemia in either SPECT or PET relative perfusion imaging. TID is probably associated with extensive ischemia and prolonged systolic dysfunction. Patients with multivessel or left main CAD have reduced left ventricular ejection fraction (LVEF) during vasodilator stress.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Diagnosis of coronary artery disease using $^{82}$Rb PET and PET/CT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>Year</td>
</tr>
<tr>
<td>Esteves[30]</td>
<td>2008</td>
</tr>
<tr>
<td>Sampson [34]</td>
<td>2007</td>
</tr>
<tr>
<td>Bateman [29]</td>
<td>2006</td>
</tr>
<tr>
<td>Williams[37]</td>
<td>1994</td>
</tr>
<tr>
<td>Marwick [33]</td>
<td>1992</td>
</tr>
<tr>
<td>Grover-McKay [32]</td>
<td>1992</td>
</tr>
<tr>
<td>Simone[35]</td>
<td>1992</td>
</tr>
<tr>
<td>Stewart [36]</td>
<td>1991</td>
</tr>
<tr>
<td>Go [31]</td>
<td>1990</td>
</tr>
<tr>
<td>Total + weighted mean</td>
<td>1151</td>
</tr>
<tr>
<td>Non-weighted mean</td>
<td></td>
</tr>
<tr>
<td>PET/CT: total weighted mean</td>
<td>251</td>
</tr>
<tr>
<td>PET: total weighted mean</td>
<td>900</td>
</tr>
</tbody>
</table>

Ado, adenosine; CAG, coronary angiography; CT, computed tomography; Dipy, dipyridamole; Dob, dobutamine; PET, positron emission tomography.

\[a\] Retrospective study.

\[b\] Other cut-offs reported.
Prognosis in coronary artery disease

Assessment of prognosis in patients with suspected or known CAD is important for patient management. SPECT MPI studies have shown excellent prognostic value, and patients with normal stress perfusion imaging have a low hard cardiac event rate (<1% year). In an early report using $^{82}$Rb, PET MPI findings were independent predictors of cardiac death and total cardiac events. The results of PET MPI had incremental prognostic value over clinical and angiographic findings alone [38]. Chow et al. showed a very low hard cardiac event rate (0.09%/year) in a group of patients with normal $^{82}$Rb PET MPI based on clinical reports [39]. Yoshinaga et al. reported that normal PET MPI had a low annual hard cardiac event rate (0.4%) and patients with a PET perfusion defect had higher hard cardiac events rates (2.3% and 7.0% for mild and moderate to severe) with stress $^{82}$Rb perfusion studies (Fig. 5A). Importantly, $^{82}$Rb PET also seems to provide prognostic value in patients whose diagnosis remains uncertain after SPECT MPI and in obese patients (Fig. 5B) [6]. This study further expands the importance of PET MPI especially in prognostic value, and PET MPI may be useful in this important population. These 3 studies represent a relatively small sample size for prognostic evaluation. A much anticipated larger sample size study was conducted by Lertsburapa et al. This study showed that integration of LV function during pharmacological stress with MPI interpretation enhanced risk stratification [5]. Changes between rest LVIF and LVIF during vasodilator stress using $^{82}$Rb gated PET were also associated with cardiac events [40]. Schenker et al. evaluated the incremental value of combining coronary artery calcium (CAC) scoring and stress/rest $^{82}$Rb PET perfusion data. A stepwise increase occurred in the risk of cardiac events with increasing CAC with and without ischemia on PET MPI [41].

Cardiac event risk over 2–3 years may be addressed in the patient report based on the following risk stratifications. ACC/AHA/ASNC guidelines recommend semi-quantitative analysis (normal perfusion = 0, mild = 1, moderate = 2, severe = 3, and absent uptake = 4) using a 17-segment model [3,42]. Using this approach, the summed perfusion defect score can be calculated, and this score system contributes a standardization of risk stratification. Yoshinaga et al. also reported that abnormal cut-off value of summed stress score ≥4 can be applied to $^{82}$Rb PET studies with the 17-segment model [6].

Clinical indication for relative perfusion imaging

The high diagnostic accuracy and prognostic values of PET MPI can contribute to better management of CAD patients. Current ACC/AHA/ASNC clinical guidelines and the joint position statement by CCS/CAR/CANM/CNCS/CanSCMR addressed that patients with an intermediate likelihood of CAD, when patients have had a non-diagnostic, equivocal SPECT MPI or other noninvasive tests, have indications for PET MPI for diagnosis and detection of ischemia as Class I indication (evidence level B) [4,42].

Assessment of absolute myocardial blood flow using $^{82}$Rb PET

Quantitative measurement of MBF is one of the great advances over PET MPI, and provides a noninvasive means to determine the functional severity of coronary stenosis [2,10,11]. While coronary angiography defines stenosis severity on the basis of morphologic alterations, the measurement of MBF or flow reserve represents a more physiological evaluation of myocardial cellular perfusion as the net result of antegrade epicardial coronary flow and collateral circulation.

Cardiovascular risk factors associated with atherosclerosis may cause reduction of coronary vasomotor function despite angiographically normal coronary arteries. PET has been used extensively to investigate the relationship of coronary vascular function and risk factors for coronary artery disease, including hypercholesterolemia, diabetes, smoking, and hypertension [2,10,11].

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Figure 5  (A) Risk-adjusted survival, free from any (total) cardiac events, as a function of summed stress score. (B) Unadjusted survival free from any (total) cardiac events as a function of normal and abnormal summed stress score on positron emission tomography myocardial perfusion imaging in patients with obesity (body mass index ≥30 kg/m$^2$) [6]. (with the permission of the author and the Journal of the American College of Cardiology).
82Rb PET MBF quantification has been applied on a limited scale, even though it is possible to quantify regional MBF as well as other PET flow tracers, such as 15O-water and 13N-ammonia [2,10,13,43].

The extraction fraction of 82Rb is 70% at rest and is relatively consistent at physiological MBF range (Fig. 1) [13]. However, the extraction decreases in a nonlinear manner at high flow range. Therefore, a flow-dependent extraction correction is required [14]. In human studies these extraction fractions are calibrated to other tracers [14,44,45] and in practice can correct for biases in the image processing workflow.

Recent studies have focused on developing MBF measurements using 82Rb. We have been witnessing much development in this field [7]. The steps toward clinical application of quantitative MBF include basic experiments, model analysis, accuracy validation with established measurements, and confirmation of repeatability of the measurements.

### Tracer kinetics

Absolute measurements of physiological or biochemical function are obtained by tracer kinetics. A parametric physical model is fit to the time–activity curves (TAC) of the arterial blood input function, Ca(t), and myocardial response function Cm(t). Ca(t) is usually measured using a region of interest (ROI) in the LV cavity, and Cm(t) is sampled in varying regions of the myocardium. The model parameters are used to estimate quantitative rate constants.

A simple net retention model can be used to calculate absolute MBF directly from short dynamic sequential images [15]. The net retention equals the measured radiotracer concentration at time t divided by the integral of the blood input function curve to that time or an earlier time point. Our group initially applied a simple net retention model for MBF quantification and then shifted to compartment models [8,46–48].

Compartment models have been developed for MBF quantification. The compartments represent tissue volumes that include physical factors (arterial blood and intracellular fluid) or biochemical factors (tracer compound and labeled metabolite). A mathematical model is constructed with parameters such as a flux of radioactivity between the compartments [49].

82Rb studies are typically modeled with a two-compartment model that includes activity in the vascular space and within the tissue compartment [50]. Following bolus injection of the tracer, predominantly unidirectional transport is assumed from the vascular space into the tissue space. A second washout parameter may also be included in the model and may be indicative of tissue viability [51].

### Validation of myocardial blood flow and assessment of repeatability

In the canine model, regional MBF can be accurately estimated using a two-compartment model of 82Rb [51]. Lautamaki et al. evaluated MBF using a simple retention approach, and there was good agreement with low variability between microsphere flow and 82Rb PET MBF in the physiological MBF range <3 mL/g/min [45]. Lortie et al. estimated 82Rb MBF using the two-compartment model and compared it to 13N-ammonia PET MBF in healthy volunteers and CAD patients. The MBF results obtained using 82Rb were correlated with those obtained using 13N-ammonia (r = 0.85) over a wide flow range [46]. Although the hyperemic MBF data measured by 82Rb was lower than that for MBF with other tracers, 82Rb MBF measurements had good correlation with 13O-water (r = 0.94) using an appropriate noise reduction approach [52]. These data validated the accuracy of 82Rb PET MBF. Table 3 summarizes the normal values in rest and hyperemic MBF in normal subjects. The average rest MBF is 0.95 mL/min/g and rest MBF is similar to MBF measured by other PET flow tracers [2,11]. On the other hand, average hyperemic MBF is 2.91 mL/min/g, which is slightly lower than that measured by other PET flow tracers usually 3.0–5.0 mL/min/g [2,11].

As the next step for clinical application, Manabe et al. evaluated the repeatability of rest and hyperemic MBF with 82Rb using 2D acquisition and a two-compartment model. MBF measurements with 82Rb showed high reproducibility with the repeatability coefficient 0.19 mL/min/g for rest and 0.92 mL/min/g for hyperemia [8]. Another approach of 82Rb MBF measurements using the two-compartment model and with factor analysis to reduce noise and spillover effects also showed good reproducibility [53].

### Assessment of myocardial blood flow in coronary artery disease

Altered MBF and flow reserve may be much more extensive than angiographic documentation of regional CAD. 82Rb MBF quantification is expected to improve the detection of multivessel CAD. Parkash et al. compared quantitative MBF and

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**Table 3** Normal values in baseline myocardial blood flow and coronary flow reserve.

<table>
<thead>
<tr>
<th>Stress agent</th>
<th>Numbers of subjects</th>
<th>Age (years)</th>
<th>Data analysis</th>
<th>MBF at rest</th>
<th>MBF at hyperemia</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin [52]</td>
<td>Dipy</td>
<td>11</td>
<td>44</td>
<td>2-comp</td>
<td>1.15 ± 0.46</td>
<td>2.50 ± 0.54</td>
</tr>
<tr>
<td>Wassenaar [48]</td>
<td>Dipy</td>
<td>15</td>
<td>34 ± 6</td>
<td>Retention</td>
<td>0.95 ± 0.35</td>
<td>3.0 ± 0.70</td>
</tr>
<tr>
<td>Lortie [46]</td>
<td>Dipy</td>
<td>14</td>
<td>31 ± 7</td>
<td>2-comp</td>
<td>0.69 ± 0.14</td>
<td>2.83 ± 0.81</td>
</tr>
<tr>
<td>Manabe [8]</td>
<td>ATP</td>
<td>15</td>
<td>29 ± 9</td>
<td>2-comp</td>
<td>0.77 ± 0.25</td>
<td>3.35 ± 1.37</td>
</tr>
<tr>
<td>El Fakhri [53]</td>
<td>Dipy</td>
<td>22</td>
<td>48 ± 12</td>
<td>2-comp</td>
<td>1.14 ± 0.19</td>
<td>2.81 ± 1.02</td>
</tr>
<tr>
<td>Total</td>
<td>Weighted mean</td>
<td>77</td>
<td>37</td>
<td>2-comp</td>
<td>0.95</td>
<td>2.91</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>77</td>
<td>37</td>
<td></td>
<td>0.94</td>
<td>2.90</td>
</tr>
</tbody>
</table>

ATP, adenosine triphosphate; CFR, coronary flow reserve; Dipy, dipyridamole; MBF, myocardial blood flow; 2-comp, two-compartment model.
Rubidium-82 positron emission tomography myocardial perfusion imaging

traditional relative perfusion assessment in patients with multivessel CAD. The defect sizes were significantly larger with the quantification approach than with the relative perfusion approach [47]. Hyperemic MBF and coronary flow reserve using $^{82}$Rb were inversely correlated with epicardial coronary artery stenosis [54]. These data agreed with previous PET studies using $^{15}$O-water and $^{13}$N-ammonia [2,11]. Accordingly, PET has been used to detect the early stages of vascular alterations and to monitor response to therapy. Van Tosh et al. [55] reported regions of abnormal flow reserve with PET $^{82}$Rb imaging and dipyridamole stress in the areas of restenosis after angioplasty. Thus, PET can be used to objectively identify patients who would benefit from revascularization and recovery of functional flow reserve.

Quantification of MBF with $^{82}$Rb PET is expected to improve with newer cameras with faster count rate capabilities by enabling injection of more activity without saturation of the camera and by supporting shorter dynamic image time frames that better measure TACs.

Coronary flow reserve in relation to coronary risk factors and evaluation of therapies

Coronary flow reserve is a complex physiological parameter influenced by many factors other than coronary artery stenosis. PET perfusion studies have demonstrated reduction of flow reserve in many cardiac disorders without evidence of coronary artery disease. As stated before, unlike other PET flow tracers, $^{82}$Rb MBF is currently being developed. Thus, evaluations of therapeutic interventions have been very limited.

Gould et al. evaluated increases in MBF reserve in association with an improvement in exercise capacity and serum lipid profiles [56]. This study evaluated myocardial perfusion abnormality using a relative perfusion uptake approach with either $^{82}$Rb or $^{13}$N-ammonia. Yoshinaga et al. evaluated the effect of exercise training on regional MBF in patients with stable CAD. The exercise training increased hyperemic MBF in diseased segments compared to those for the sedentary lifestyle group (% increase in myocardial blood flow: $12.5 \pm 22.1\%$ vs. $2.6 \pm 16.3\%, p = 0.02$) (Fig. 6A and B) [57]. These data may indicate favorable evidence to support the effect of exercise training on MBF to ischemic myocardium. Ling et al. evaluated the effects of statin therapy on peripheral endothelial function and coronary vascular function. Simvastatin improved peripheral endothelial function but did not improve coronary flow reserve [58].

Endothelial dysfunction in patients who have coronary risk factors

Coronary endothelial dysfunction is one of the earliest abnormalities to be seen in the development of CAD. Endothelial dysfunction is considered to be associated with future cardiac events. PET MPI with cold pressor tests has also been applied to measure coronary endothelial function noninvasively [2,11,12]. Preliminary data by Yoshinaga et al. reported that normal subjects increased MBF during cold pressor test [59]. These data need further study and further investigations are currently underway.

Summary

PET MPI provides accurate evaluation of regional MBF at rest and during stress. The role of $^{82}$Rb PET myocardial perfusion imaging is now well established for diagnosis and risk stratification of CAD. In the past, widespread clinical use has been limited by the cost of the technology and access to the radiotracers. However, $^{82}$Rb PET has greatly contributed to increasing acceptance of PET for clinical practice. This trend is expected to continue not only in North America, but also in Asia and Europe.

MBF quantification using $^{82}$Rb PET has undergone extensive development in recent years. Application of MBF for the assessment of therapeutic interventions in subjects with coronary arteriosclerosis risk is expected. $^{82}$Rb PET imaging may also be used for endothelial function measurements capable of defining early stage coronary arteriosclerosis. More studies are needed to establish this measurement. We hope this hybrid approach will help optimize clinical decision-making for therapy selection and this will improve patient outcomes.

Figure 6

(A) A patient with exercise training (top) improved hyperemic myocardial blood flow in the lateral area. In contrast, there was no significant difference between baseline and follow-up in the control patient. (B) Exercise training significantly increased hyperemic myocardial blood flow and hence coronary flow reserve [57] (with the permission of the author and the American Heart Journal).
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References


