

5 Radiopharmaceuticals for Clinical Cardiac PET Imaging

Josef Machac

The clinical value of cardiac positron emission tomography (PET) imaging was demonstrated more than 20 years ago,¹⁻³ but its clinical utilization has been low until recently. This was due to the limitation of PET imaging to research centers with a PET camera and a cyclotron, its great expense, and the lack of reimbursement for clinical PET studies. Another disincentive was lack of standardized software for cardiac PET image processing, display, or regional quantification on most PET imaging systems.

There is now an extensive infrastructure in PET imaging with an extensive network of PET and PET/CT cameras installed throughout North America. Myocardial PET perfusion imaging with rubidium-82 (⁸²Rb), reimbursed by the Centers for Medicare and Medicaid Services (CMS) since 1995, can be performed with a commercially available generator, obviating the need for a cyclotron. More recently, mobile ⁸²Rb generators have become available in some regions, allowing PET centers that are not financially able to support a 7-day-a-week ⁸²Rb service to offer PET myocardial perfusion imaging only one to several times a week. All metropolitan areas in North America now have at least one commercial F-18 fluorodeoxyglucose (FDG) supplier. FDG PET imaging is now reimbursed for myocardial viability imaging. More recently, CMS reimbursement has become available for myocardial perfusion imaging with nitrogen-13 (¹³N) ammonia for those centers that do have a cyclotron that could until recently offer PET myocardial perfusion imaging only for patients who could afford to pay for the procedure or who participated in a funded research study.

The widespread installation of PET-CT cameras represents another leap forward. The use of CT for attenuation correction substantially shortens the acquisition time for a clinical study. The combination of PET scanners with 16-or-more-slice multidetector CT scanners offers the tantalizing possibilities of PET perfusion and viability imaging in concert with coronary calcium scoring and coronary CT angiography, which potentially represents a one-stop service. This chapter reviews the characteristics of the available radiotracers for cardiac PET imaging.

Myocardial PET Perfusion Tracers

Nitrogen-13 Ammonia

Nitrogen-13 ammonia has been used for most of the scientific investigations in cardiac PET imaging over the past two decades. Its 9.96-minute half-life (Table 5.1) requires an on-site cyclotron and radiochemistry synthesis capability. Nitrogen-13 is produced

TABLE 5.1. Characteristics of Cardiac PET Tracers

Agent	Physical Half-life ⁴⁶	Mean Positron Range (mm) ^{47,48,49}	Production	Extraction
N-13 NH ₃	9.96 min	0.7	Cyclotron	80% ⁵⁰
⁸² Rb	76s	2.6	Generator	50%–60% ⁵¹
F-18 FDG	110 min	0.2	Cyclotron	1%–3% ⁵²

by bombarding O-16 water with 16.5 MeV protons via the $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ reaction. The target material is made of aluminum, although targets made of nickel or titanium can also be used. Two methods can be used for ^{13}N -ammonia synthesis. In the first method, the ^{13}N -labeled nitrates/nitrites formed by proton irradiation of water are reduced by either titanium (III) chloride, titanium (III) hydroxide, or Devarda's alloy in alkaline medium.⁴ After distillation, trapping, and sterile filtration, ^{13}N -ammonia is ready for injection. In the second method, oxidation of ^{13}N to ^{13}N -nitrates/nitrites is prevented by the addition of ethanol as a scavenger to the target content.⁵ The target content is passed through a small cation-exchange column to trap ^{13}N -ammonium ions, and ^{13}N -ammonia is then eluted with saline and filtered.

In the bloodstream, ^{13}N -ammonia consists of neutral NH_3 in equilibrium with its charged ammonium (NH_4^+) ion (Figure 5.1). The neutral NH_3 molecule readily diffuses across plasma and cell membranes, leading to virtually complete extraction from the vascular pool. Inside the myocyte, it re-equilibrates with its ammonium form, which is trapped in glutamine via the enzyme glutamine synthase.^{6,7} Figures 5.2 and 5.3 show the kinetics of ^{13}N -ammonia in plasma and myocardium. Backdiffusion of ^{13}N -ammonia is proportional to blood flow and limits effective trapping.⁷ Despite backdiffusion, the first-pass trapping of ^{13}N -ammonia at rest is high (Table 5.1), although, like other extractable tracers, it decreases at higher blood-flow rates (Figure 5.4). The overall trapping of ^{13}N -ammonia relies on intact metabolism, which may be impaired in ischemia and high cardiac work.

Myocardial retention of ^{13}N -ammonia may be heterogeneous; retention in the lateral wall of the left ventricle even in normal subjects is about 10% less than that of other segments. The mechanism of this finding is not known.⁹ ^{13}N -ammonia images also may be degraded by occasional intense liver activity, which can interfere with the

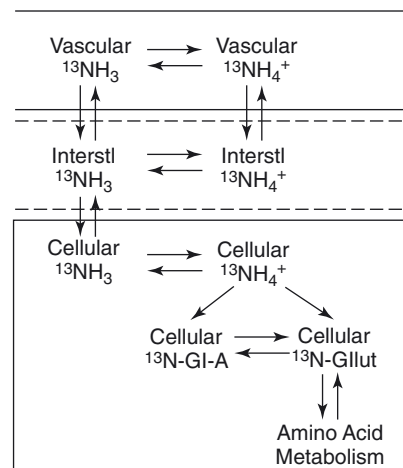


FIGURE 5.1. Schema of ^{13}N -ammonia in plasma and transport into tissue followed by metabolic trapping.

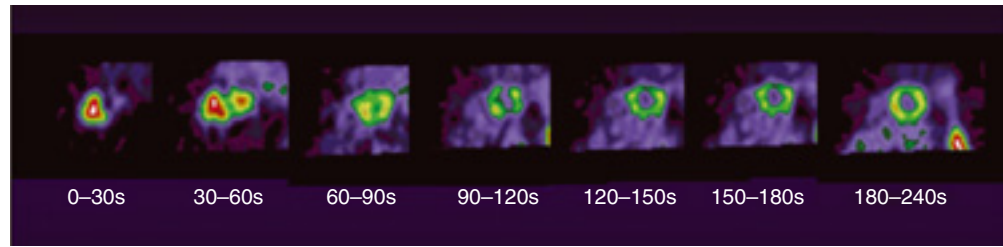


FIGURE 5.2. Serial PET images of cardiac blood clearance and uptake of ^{13}N -ammonia in a human subject. (Courtesy of Robert Gropler, MD.)

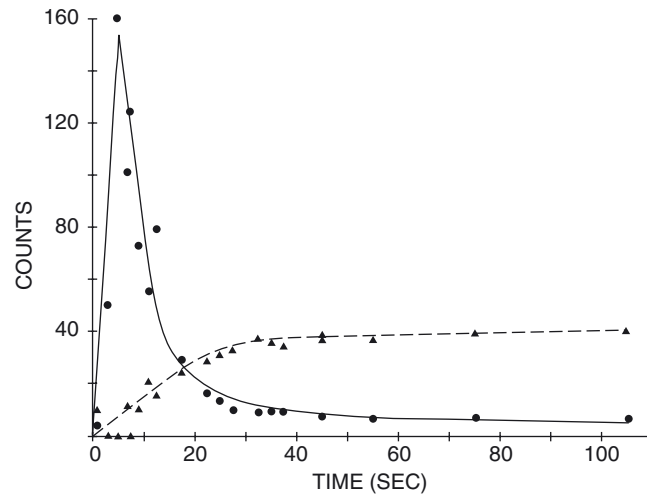


FIGURE 5.3. Plasma and myocardial kinetics of ^{13}N -ammonia in a dog, which shows faster circulation kinetics than humans. (Reproduced with permission from Schelbert HR and Schwaiger M. 1986, 581–661 (8).)

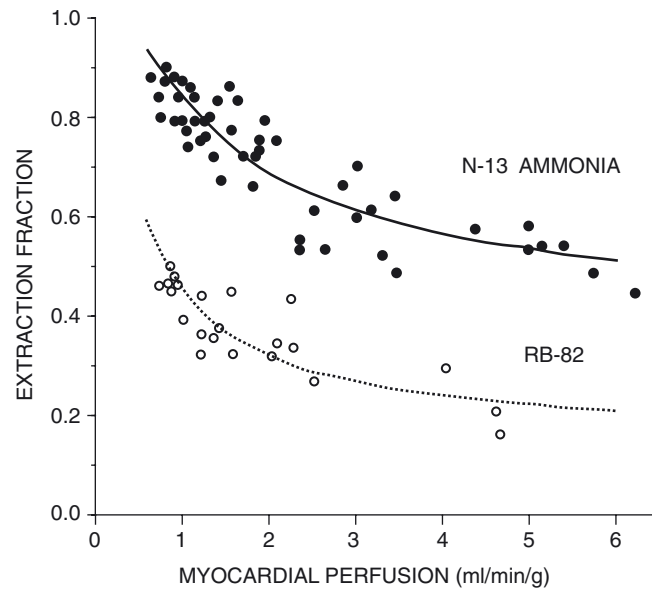


FIGURE 5.4. The relationship between uptake extraction fraction and myocardial perfusion for ^{13}N -ammonia and ^{82}Rb . As myocardial blood flow increases from 0.5 to 6.0 mL/min/g, extraction fraction decreases. (Reprinted by permission of the Society of Nuclear Medicine from: K Yoshida, N Mullani, and KL Gould. Coronary flow and flow reserve by PET simplified for clinical applications using rubidium-82 or nitrogen-13-ammonia. J Nucl Med. 1996;37:1701–1712. Figure 9.)

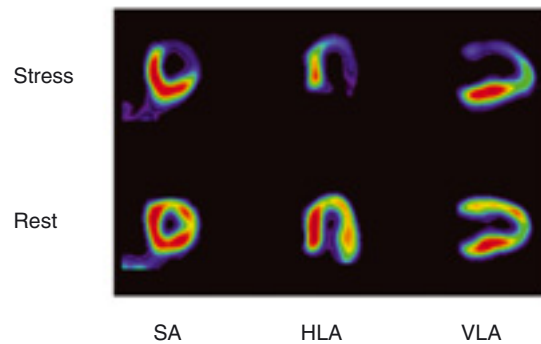


FIGURE 5.5. ^{13}N -ammonia PET images demonstrating anterior and lateral defects during pharmacological stress and significant improvement at rest, consistent with ischemia. SA, short axis; HLA, horizontal long axis; VLA, vertical long axis. (Courtesy of Dr. H Schelbert.)

evaluation of the inferior wall. Although the sequestration of ^{13}N -ammonia in the lungs is usually minimal, it may be increased in patients with depressed left ventricular systolic function or chronic pulmonary disease and, occasionally, in smokers.¹¹ In these cases, it may be necessary to increase the time between injection and image acquisition to optimize the contrast between myocardial and background activity.

^{13}N -ammonia allows the acquisition of good-quality ungated (Figure 5.5) and gated images. It takes full advantage of the superior resolution of PET relative to SPECT imaging, stemming from a sufficiently long half-life and the very short path length of the positrons emitted by ^{13}N (Table 5.1). Gated ^{13}N -ammonia imaging can produce accurate assessments of regional and global cardiac function.¹²

Rubidium-82

Rubidium-82 (^{82}Rb) is a monovalent cationic analogue of potassium that is produced in a commercially available generator by decay from strontium-82 (^{82}Sr) attached to an elution column. The ^{82}Sr is produced in a cyclotron by proton spallation of molybdenum with a high-energy (800 MeV) accelerator, followed by chemical purification.¹³ The ^{82}Sr has a half-life of 25.5 days and decays to ^{82}Rb by electron capture. The physical half-life of ^{82}Rb is 76 seconds, and it decays into krypton-82, which is stable, by emitting a positron and a neutrino.

Figures 5.6 and 5.7 illustrate the generator and delivery system for ^{82}Rb , consisting of a cabinet, an ^{82}Rb generator, a pump, control electronics, and connecting tubing.

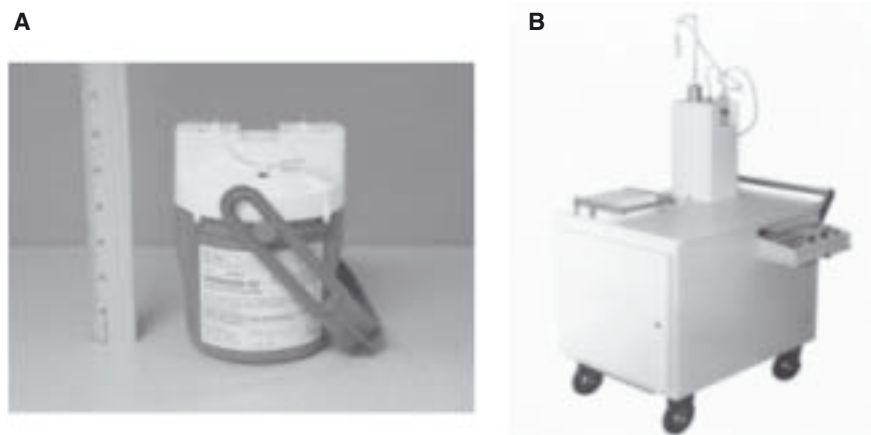


FIGURE 5.6. (A) ^{82}Rb generator. (B) ^{82}Rb delivery system. (Equipment by Bracco Diagnostics.)

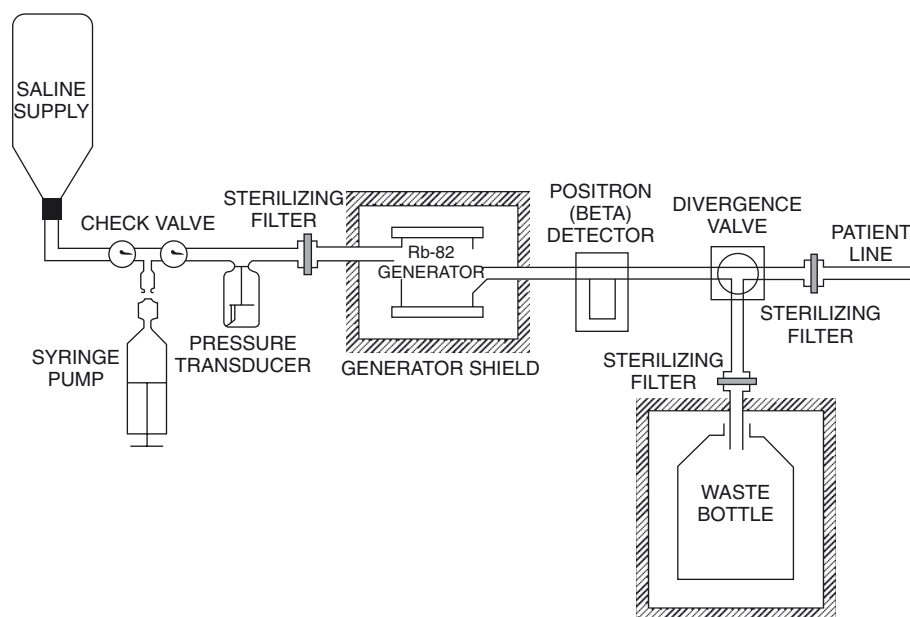


FIGURE 5.7. Schematic of an ^{82}Rb delivery system.

With a half-life of 25 days, the ^{82}Sr -containing generator is replaced every 4 weeks. Rubidium-82 is eluted with 25 to 50 cc normal saline by a computer-controlled elution pump, connected by IV tubing to the patient. The generator is fully replenished every 10 minutes; our experiments have shown that 90% of maximal available activity can be obtained within 5 minutes since the last elution.¹⁴ Thus, serial imaging can be performed every 5 minutes. Although the short half-life of ^{82}Rb taxes the performance limits of PET scanners, it facilitates the rapid completion of a series of resting and stress myocardial perfusion studies. Rubidium-82 is a very efficient imaging agent for routine clinical usage. Because of the short half-life of ^{82}Rb and the need for the patient to lie still in the camera during the study, stress imaging of this agent is limited to pharmacological stress, although studies have obtained serviceable ^{82}Rb images with supine bicycle exercise or even treadmill exercise.¹⁵

Rubidium-82 is extracted from plasma with high efficiency by myocardial cells via the Na^+/K^+ ATPase pump (Figure 5.8). Myocardial extraction of ^{82}Rb is similar to that of thallium-201 (^{201}Tl)^{16,17} and slightly less than ^{13}N -ammonia (Table 5.1; Figure 5.4). Figure 5.9 shows serial images of blood pool and myocardial ^{82}Rb activity in the first several minutes after injection, and Figure 5.10 shows plasma and myocardial

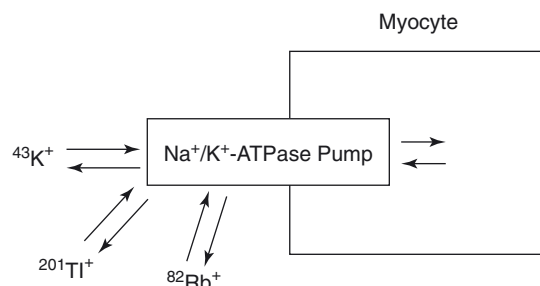


FIGURE 5.8. Diagram of myocardial uptake mechanism of monovalent cations K -43, Tl -201, and ^{82}Rb .

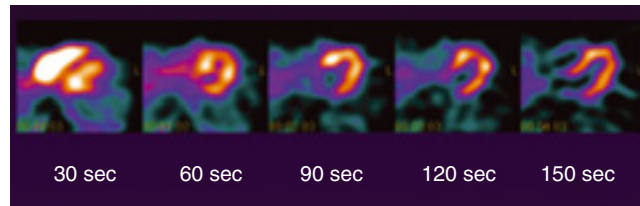


FIGURE 5.9. Serial PET images of blood pool and myocardial ^{82}Rb activity in the first 3 minutes after injection. (Mount Sinai School of Medicine, New York.)

^{82}Rb kinetics. Extraction decreases with increasing blood flow^{18,19} (Figure 5.4). In addition, ^{82}Rb extraction can be decreased by severe acidosis, hypoxia, and ischemia.^{20–22} Thus, uptake of ^{82}Rb is a function of blood flow, metabolism, and myocardial cell integrity.

In spite of the short half-life of ^{82}Rb , modern PET gamma cameras are able to obtain good-quality images (Figure 5.11). Imaging with ^{82}Rb is not able to take full advantage of the superior resolution of PET because of the relatively long mean path of 2.6 mm of the energetic ^{82}Rb positrons and the need for filtering required to obtain optimal images with the short-lived tracer.

Oxygen-15 Water

Oxygen-15 water (^{15}O -water) is a cyclotron product with a physical half-life of 2.07 minutes. Oxygen-15 water is a freely diffusible agent with very high myocardial extraction across a wide range of myocardial blood flows.²³ The degree of extraction is independent of flow and is not affected by the metabolic state of the myocardium.²³ Because it is a freely diffusible tracer, however, imaging is challenging due to its high concentration in the blood pool. This requires subtraction of the blood pool counts from the original image to visualize the myocardium. This can be accomplished by acquiring a second set of images after a single inhalation 40 to 50 mCi of ^{15}O -carbon monoxide (^{15}CO). Oxygen-15 carbon monoxide binds irreversibly to hemoglobin, forming ^{15}O -carboxyhemoglobin and thereby allowing delineation and digital subtraction of blood pool activity. The cumbersome nature of the procedure required to subtract blood pool activity of ^{15}O -water to visualize the myocardium has limited the use of this tracer in the clinical setting.

Selecting a Perfusion Tracer for Clinical Cardiac PET

Although in many ways ^{15}O -water is an ideal flow tracer, its use in the clinical setting remains limited. Besides requiring an on-site cyclotron, obtaining diagnostic

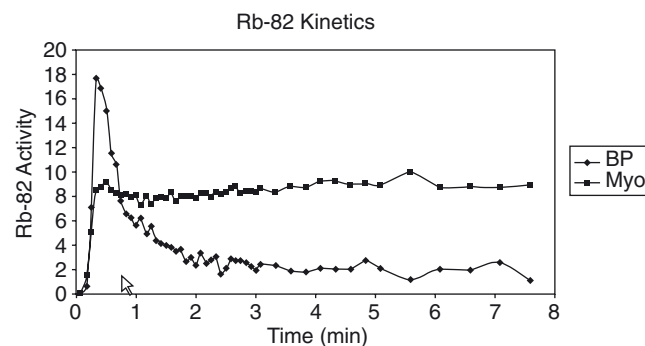


FIGURE 5.10. Kinetics of blood pool and myocardial ^{82}Rb activity. (Mount Sinai School of Medicine, New York.)

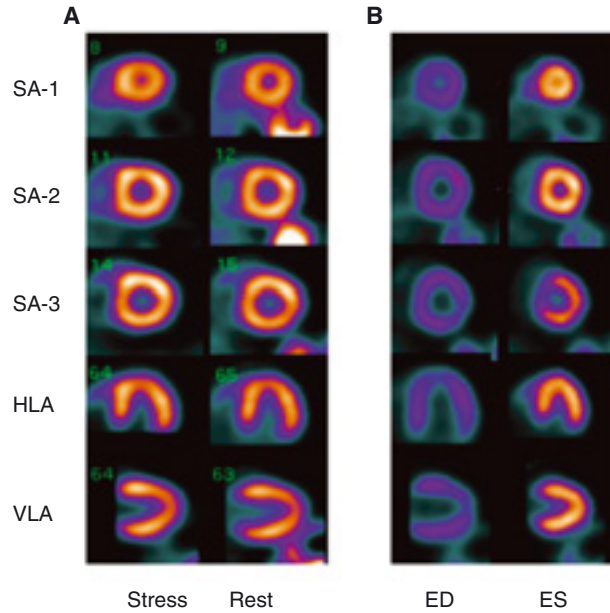


FIGURE 5.11. A. Normal stress and rest ^{82}Rb PET images. B. Resting end-diastolic (ED) and end-systolic (ES) gated images, showing uniformly good contractility. (Mount Sinai School of Medicine, New York.)

images requires an impractical image subtraction procedure. The advantages of ^{13}N -ammonia are its higher first-pass tissue extraction (65% to 70%) compared to ^{82}Rb (60% to 65%)^{10,19,22,24} and a longer half-life, which allows longer imaging times and better count statistics, as well as injection during treadmill exercise and subsequent imaging of the trapped radionuclide in the myocardium. However, the main disadvantage of ^{13}N -ammonia vis-à-vis ^{82}Rb is the need for an on-site cyclotron, which makes it costly and impractical. Also, the longer physical half-life of ^{13}N -ammonia makes rest-stress protocols more inefficient than with ^{82}Rb (~90 minutes vs 30 minutes, respectively). Finally, increased uptake in the liver and, occasionally, in the lungs (as in patients with heart failure and smokers) can adversely affect image quality.

Imaging of Myocardial Metabolism

Fluorine-18 Fluorodeoxyglucose

Preserved metabolism for the production of ATP is one of the critical features of myocardial viability. Fluorine-18 (^{18}F) fluorodeoxyglucose (FDG) is fluorine-18-labeled 2-deoxyglucose, an analogue of glucose. Fluorine-18 is produced in a cyclotron through the (p,n) reaction, consisting of bombardment of O-18-enriched water with a proton beam with energies less than 15 MeV. High specific activity of ^{18}F fluorine is thus obtained. F-18 FDG is prepared by nucleophilic substitution on a tetraacetylmannose triflate precursor. This yields large quantities of pure D-FDG.²⁵

Fluorine-18 fluorine decays by the emission of a positron and a neutrino, whereby the ^{18}F fluorine decays to O-18 oxygen. The low kinetic energy of the positron, 635 keV, allows the highest spatial resolution among the commonly used PET radionuclides (Table 5.1). The relatively longer half-life of ^{18}F of 109.8 minutes allows sufficient time for synthesis of ^{18}F FDG, its commercial distribution in a radius of several hours from the production site, its temporary storage at the user site, the 30 to 60 minutes of

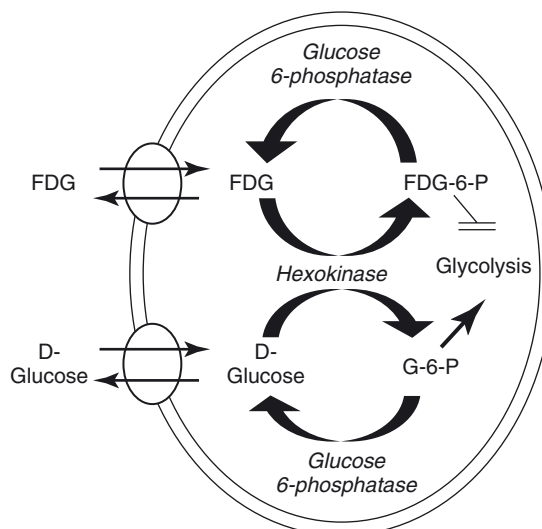


FIGURE 5.12. Schematic diagram of cellular FDG uptake and retention. (From Machac J. Gated positron emission tomography for the assessment of myocardial perfusion and function. In: Clinical gated cardiac SPECT. Germano G, Berman DS, eds, Blackwell Futura, 2006. Reprinted with permission.)

absorption time after injection, and sufficient imaging time to yield images of high quality. At the same time, it does lead to higher radiation exposure, for any given dose, compared to shorter-lived radiotracers, but at the same time similar to that of Tc-99m perfusion agents and lower than a clinical dose of ^{201}Tl .

Like D-glucose, FDG is transported into the myocardium by specific glucose transporters (GLUT-1 and GLUT-4) by facilitated diffusion (Figure 5.12). Inside the cell, FDG undergoes phosphorylation by the enzyme hexokinase. Because of very low levels of the enzyme glucose-6-phosphatase catalyzing the reverse reaction, FDG is essentially trapped in the cell.²⁶ It has been demonstrated that in a metabolic steady state, FDG uptake in the myocardium correlates linearly with uptake and utilization of exogenous glucose.²⁷

Following injection, FDG is slowly taken up by body tissues, including the myocardium (Figures 5.13 and 5.14). Imaging is performed about 45 to 90 minutes after injection. As a result, the 110-minute physical half-life of ^{18}F FDG is well-suited for viability imaging (Table 5.1).

Summary Points

- There are a limited number of well-characterized PET radiopharmaceuticals for clinical imaging. Their short physical half-life allows rapid sequential imaging of

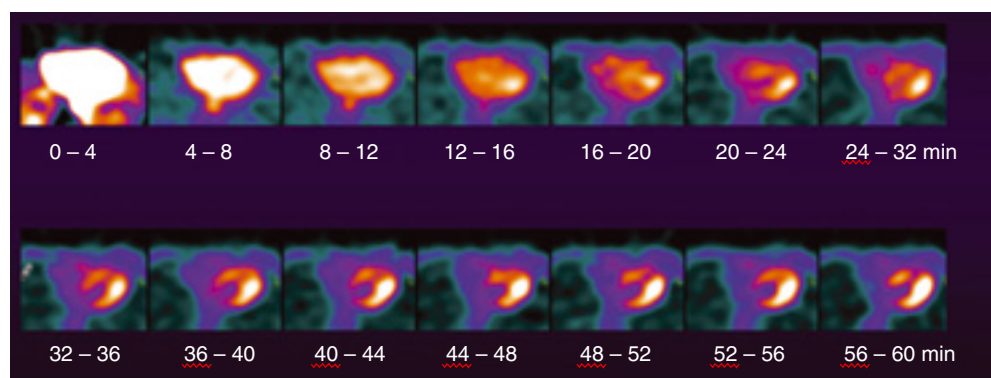


FIGURE 5.13. Serial dynamic images of plasma and myocardial ^{18}F FDG activity. (Mount Sinai School of Medicine, New York.)

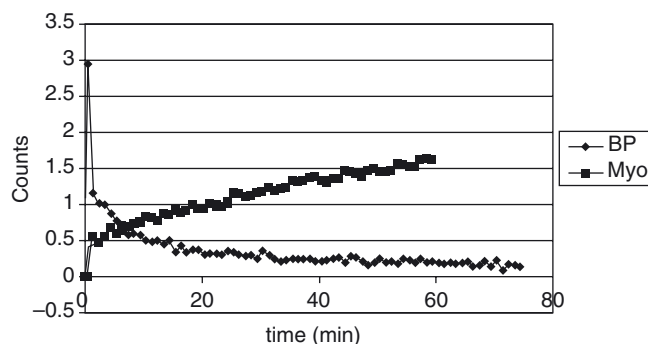


FIGURE 5.14. Kinetics of blood pool (BP) and myocardial (Myo) ^{18}F FDG activity. (Mount Sinai School of Medicine, New York.)

rest and stress perfusion imaging, which is more efficient and accurate than SPECT imaging.

- The known tracer kinetics of PET radiopharmaceuticals, coupled with the technical advantages of PET (e.g., attenuation correction, high temporal resolution), allow quantitation of myocardial blood flow that can be used to improve diagnosis of coronary artery disease (see Chapters 11 and 12).
- The main disadvantage of the available tracers is cost. As clinical PET expands its role into cardiac imaging, we will probably see significant investments in research and development of long-lived (e.g., ^{18}F) perfusion agents than could potentially be distributed by unit doses, similar to the successful model of ^{18}F FDG.

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