Cardiac Positron Emission Tomography Imaging

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Cardiac positron emission tomography (PET) imaging has advanced from primarily a research tool to a practical, high-performance clinical imaging modality. The widespread availability of state-of-the-art PET gamma cameras, the commercial availability of perfusion and viability PET imaging tracers, reimbursement for PET perfusion and viability procedures by government and private health insurance plans, and the availability of computer software for image display of perfusion, wall motion, and viability images have all been a key to cardiac PET imaging becoming a routine clinical tool. Although myocardial perfusion PET imaging is an option for all patients requiring stress perfusion imaging, there are identifiable patient groups difficult to image with conventional single-photon emission computed tomography imaging that are particularly likely to benefit from PET imaging, such as obese patients, women, patients with previous nondiagnostic tests, and patients with poor left ventricular function attributable to coronary artery disease considered for revascularization. Myocardial PET perfusion imaging with rubidium-82 is noteworthy for high efficiency, rapid throughput, and in a high-volume setting, low operational costs. PET metabolic viability imaging continues to be a noninvasive standard for diagnosis of viability imaging. Cardiac PET imaging has been shown to be cost-effective. The potential of routine quantification of resting and stress blood flow and coronary flow reserve in response to pharmacologic and cold-pressor stress offers tantalizing possibilities of enhancing the power of PET myocardial perfusion imaging. This can be achieved by providing assurance of stress quality control, in enhancing diagnosis and risk stratification in patients with coronary artery disease, and expanding diagnostic imaging into the realm of detection of early coronary artery disease and endothelial dysfunction subject to risk factor modification. Combined PET and x-ray computed tomography imaging (PET-CT) results in enhanced patient throughput and efficiency. The combination of multislice computed tomography scanners with PET opens possibilities of adding coronary calcium scoring and noninvasive coronary angiography to myocardial perfusion imaging and quantification. Evaluation of the clinical role of these creative new possibilities warrants investigation.
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Why Cardiac Positron Emission Tomography (PET)?

Coronary artery disease (CAD) continues to be a leading cause of death in modern industrialized countries. A steady growth in the use of myocardial single-photon emission computed tomography (SPECT) perfusion imaging has been charted in the past 2 decades and, as a result, SPECT has become an important component of the clinical management of this disease. This is attributable to its high success rate in providing useful information about myocardial perfusion and function.

Despite the success of cardiac SPECT imaging, room for significant improvement still exists. Despite a high sensitivity of 90% to 94% for multivessel coronary disease, conventional SPECT imaging has a limited sensitivity of 60% to 76% for detecting significant single-vessel disease.[1,2] The presence of diffuse disease in all 3 coronary vessels may decrease the sensitivity for each individual vessel, and "balanced ischemia" may mask the presence of disease altogether.[3-7] Diffuse coronary artery disease without segmental stenosis frequently is the substrate for plaque rupture and coronary events.[8-10] Identification of early disease is a target of intervention through diet, glycemic control, lifestyle changes, and pharmacologic therapy.[11-16] The detection of preclinical coronary disease by conventional radionuclide imaging is limited by incomplete extraction of tracer by the myocardium

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Table 1 Cardiac PET Tracers

Agent	Physical half-life[215]	Mean positron range (mm)[216-218]	Production	Extraction
^{13}N NH$_3$	10.0 min	0.7	Cyclotron	80%[219]
^{82}Rb	78 s	2.6	Generator	50-60%[220]
^{15}O H$_2$O	2.0 min	1.1	Cyclotron	Diffusible
^{18}F FDG	110 min	0.2	Cyclotron	1-3%[221]

during first passage[17-19] and by the absence of hemodynamically significant coronary obstruction.

The use of vasodilator stress agents like dipyridamole or adenosine, which are used in approximately 40% of all stress imaging procedures, does not provide independent information about the adequacy of the vasodilator stress. Despite a high overall effectiveness, the surreptitious use of caffeine, diffuse epicardial disease, or diffuse small vessel disease may contribute to slightly decreased negative prognostic predictive value of pharmacologic myocardial perfusion imaging compared with exercise.[20] Our reliance on relative regional deficiencies in perfusion may mask a uniformly poor response to vasodilatory stimulation.

SPECT imaging also is limited by artifacts stemming from nonuniform attenuation. The recognition of attenuation artifacts through intensive training, experience, and the use of gated SPECT imaging,[21] still leaves a frequent uncertainty about possible underlying CAD in the presence of artifact.[22,23]

Another area of possible improvement is the relative low efficiency of conventional gamma cameras. Coupled with a limit on the maximal dose of radiotracer, there is a lower limit on the time required for image acquisition. From the patient's point of view, common acquisition protocols take several hours to complete. The half-lives of currently used radioisotopes limit the number of repeat tracer injections.

Recent Changes in the Status of PET Imaging

Despite the fact that the clinical value of cardiac PET imaging was demonstrated 20 years ago,[24-26] its clinical use has been minimal. The clinical impracticality of PET included limitation to a few research centers, the need for a cyclotron, the expense of PET, lack of reimbursement, and limited availability of user-friendly software for cardiac image processing and display, with a few exceptions.

All of that has changed. With more than 1000 PET cameras installed in North America (GE Medical Systems, personal communication, 2004), there is an extensive infrastructure in PET imaging. With an average use of only 4 oncologic studies being performed per PET scanner per day (GE Medical Systems, personal communication, 2004), there is potential for part-time availability of most PET scanners for cardiac imaging. Myocardial PET perfusion imaging with rubidium-82 (^{82}Rb), reimbursed by the Center for Medicaid and Medicare Services (CMS) since 1995, is possible with a commercially available generator. Mobile ^{82}Rb generators are available in some regions for centers that choose to offer PET myocardial perfusion imaging only one to several times a week. ^{18}F fluorodeoxyglucose (FDG) PET imaging is now reimbursed for myocardial viability. Metropolitan areas in North America now have at least one commercial supplier of FDG. More recently, CMS reimbursement became available for myocardial perfusion imaging with ^{13}N ammonia.

The Power of PET Imaging

PET imaging differs from conventional radionuclide imaging because it uses radionuclides that decay with positron emission. A positron has the same mass as an electron but has a positive charge. The positron travels a short distance, up to a few millimeters, interacts with an electron, and the two undergo a mutual annihilation, resulting in the production of 2 511-kev gamma photons, 180° apart form each other. PET imaging consists of detection of these photons in coincidence. Imaging by PET with electronic coincidence localization using a ring detector leads to high acquisition efficiency. This results in high-quality images acquired in a short time and multiple sequential acquisitions. The short half-lives of ^{82}Rb and ^{13}N ammonia (Table 1) result in low radiation exposure for the patient (Table 2) from multiple intervention studies or follow-up studies and allow other radionuclide imaging studies on the same day. High image uniformity is a result of the ability of PET to perform effective nonuniform attenuation correction, thus minimizing attenuation artifact. The ability to calibrate the PET system allows quantification of myocardial flow and glucose utilization.

Table 2 Cardiac PET Tracer Dosimetry[222]

Agent	Activity (mCi)	EDE (rem)	Critical Organ	Organ Dose (rem)
^{13}N NH$_3$	20	0.166	Bladder	0.52
^{82}Rb	60	0.096[240]	Kidneys	1.98
^{15}O H$_2$O	60	0.252	Heart	0.49
^{18}F FDG	10	1.100	Bladder	7.00

Table 3 Imaging Protocol for ^{13}N Ammonia PET Imaging

Procedure	Time
Positioning (Scout)	5 min
Transmission imaging	10 min
Injection and blood clearance	5 min
Rest gated perfusion imaging	10-20 min
^{13}N decay waiting time	45 min
Pharmacological stress	7 min
Injection and blood clearance	5 min
Stress imaging	10-20 min
Total duration	100-120 min

PET imaging offers a potentially high resolution of 5 to 7 mm, compared with 15 mm with SPECT imaging,[27] although in cardiac imaging, resolution is degraded by respiratory and cardiac wall movement. Cardiac imaging offers some but not the full potential resolution of PET.

Myocardial PET Perfusion Tracers and Imaging Protocols

^{13}N Ammonia

The principal cardiac PET radiotracers are listed in Tables 1 and 2. ^{13}N ammonia has been used for most of the scientific investigations in cardiac PET imaging for the past 2 decades. Its 10-minute half-life requires an on-site cyclotron and radiochemistry synthesis capability. A sample imaging protocol is given in Table 3. Pharmacologic stress imaging usually follows resting injection and imaging, after the initial activity has been allowed to decay, by staggering patients, or using differential doses for rest and stress. Both rest and stress images can be gated. A dynamic acquisition is acquired for the quantification of blood flow. This can be accomplished by performing separate dynamic and gated acquisitions with the same injection, or through list-mode acquisition. A third injection may be included for cold-pressor testing. ^{13}N ammonia imaging requires coordinating the activities of at least 4 people; the cyclotron operator, the radiochemist, the PET technologist, and the supervising physician. It can be a daunting task with a large number of rest and stress ^{13}N ammonia studies on the same day.

In the bloodstream, ^{13}N ammonia consists of neutral ammonia (NH_3) in equilibrium with its charged ammonium (NH_4) ion. The neutral NH_3 molecule readily diffuses across plasma and cell membranes. Inside the cell, it re-equilibrates with its ammonium form, which is trapped in glutamine via the enzyme glutamine synthase.[28,29] Despite back diffusion, the first-pass trapping of ^{13}N ammonia at rest is high, although decreasing with higher blood flow.

^{13}N ammonia allows good quality gated and ungated images (Fig. 1), taking full advantage of the superior resolution of PET imaging. Interestingly, normal volunteers show mild heterogeneity or mild defects of ^{13}N ammonia retention in the lateral wall of the left ventricle compared with the other segments. The mechanism of this finding is not known.[30] This must be taken into account for both visual and quantitative analysis. ^{13}N ammonia images may be degraded by occasional intense liver activity, and increased lung activity in patients with lung congestion.[31]

Oxygen-15 (^{15}O) Water

^{15}O water is neither an approved tracer nor reimbursed for clinical imaging in the United States but is included in this review as an important tracer for quantitative investigations of myocardial blood flow.[32] The ability of water to diffuse freely across plasma membranes makes this tracer a favorite for quantitation of myocardial blood flow. However, this very property leads to poor contrast between the myocardium and cardiac blood pool, requiring subtraction of blood pool activity. The use of ^{15}O water is restricted to sites with a cyclotron.

Rubidium-82 (^{82}Rb)

^{82}Rb is produced in a commercially available generator by decay from strontium-82 attached to an elution column. ^{82}Rb is eluted with 25 to 50 mL of normal saline by a computer-controlled elution pump, connected by IV tubing to the patient. The strontium-82 containing generator is replaced every 4 weeks ($t_{1/2}$ = 25 days). ^{82}Rb decays by positron emission with a short half-life of 75 s (Table 1). The generator is fully replenished every 10 minutes, and 90% of maximal available activity can be obtained within 5 minutes after the last elution.[33] Whereas 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 (Tables 4 and 5). Thus, ^{82}Rb is a very efficient imaging agent for routine clinical usage. The fixed cost of the ^{82}Rb generator may be an initial hurdle. Although the cost per patient at a low volume of studies per day is high, the cost with 6 to 10 studies per day is competitive with SPECT tracers.

^{82}Rb, like thallium-201, is a cation and an analog of potassium. It is extracted from plasma by myocardial cells via the Na^+/K^+ ATPase pump. Myocardial extraction of ^{82}Rb is similar to thallium-201 (^{201}Tl)[34,35] and slightly less than N-13 ammonia (Table 1), decreasing during hyperemia.[36,37] ^{82}Rb extraction can be altered by severe acidosis, hypoxia, and
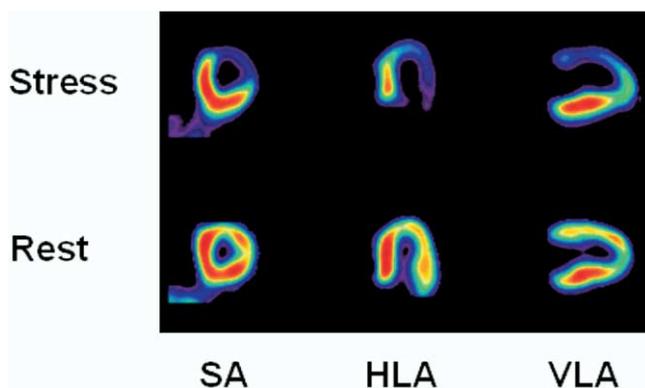
Figure 1 ^{13}N Ammonia PET images demonstrating anterior and lateral defects during pharmacological stress and significant improvement at rest, consistent with ischemia. SA, short axis; HLA, horizontal long axis; VLA, vertical long axis (courtesy of Dr. H Schelbert, UCLA School of Medicine, CA).

Table 4 Imaging Protocol for [82]Rb PET Imaging With a Bismuth Germanate (BGO) Crystal PET Scanner (the Mount Sinai Medical Center, NY)

Procedure	Time
Positioning (Scout)	5 min
Rest gated imaging	8 min
Rest perfusion imaging	8 min
Transmission imaging	8 min
Pharmacological stress	7 min
Stress imaging	8 min
Total duration	44 min

ischemia.[38-40] Thus, uptake of [82]Rb is a function of both blood flow and of myocardial cell integrity.

Patient Preparation and Stress Testing

Patient preparation for stress and rest myocardial PET perfusion imaging is identical to SPECT perfusion imaging. Myocardial PET perfusion imaging usually is performed with pharmacologic stress, primarily with dipyridamole or adenosine, despite the fact that ^{13}N ammonia imaging is feasible with treadmill stress testing and despite isolated satisfactory results with exercise using [15]O water[41] or [82]Rb.[42]

Imaging of [82]Rb

Despite the short half-life of [82]Rb, modern PET gamma cameras are able to obtain good quality images (Figs. 2 and 3). Imaging with [82]Rb does not take full advantage of the superior resolution of PET because of the relatively long mean path (2.6 mm) of the energetic [82]Rb positrons (Table 1) and due to the need for filtering with the short-lived tracer.

Our protocol (Table 4) begins with a low dose ([20m]Ci) injection of [82]Rb and a short 3-min scout acquisition and quick reconstruction for proper positioning. The patient then receives a 50- to 60-mCi dose at rest, acquired in 2D gated mode for 6 min beginning at 2 min after the onset of injection. This is followed by another 50- to 60-mCi injection, at rest, using a phasic (dynamic), 8-min acquisition, for perfusion imaging. The dynamic acquisition allows a retrospective selection of the onset of the myocardial phase, which is delayed in heart failure, low cardiac output, or poor bolus quality, and allows blood flow quantification. This is followed by an 8-min transmission scan with a germanium-68 pin source. The patient then undergoes pharmacologic stress. At peak

Table 5 Imaging Protocol for [82]Rb PET Imaging With Lutetium Orthosilicate (LSO) Crystal PET Scanner[223]

Procedure	Time
Rest transmission imaging	4 min
Rest perfusion 2D imaging	5 min
Rest gated 3D imaging	3 min
Pharmacological stress	7 min
Stress transmission imaging	4 min
Stress perfusion 2D imaging	5 min
Stress gated 3D imaging	3 min
Total duration	31 min
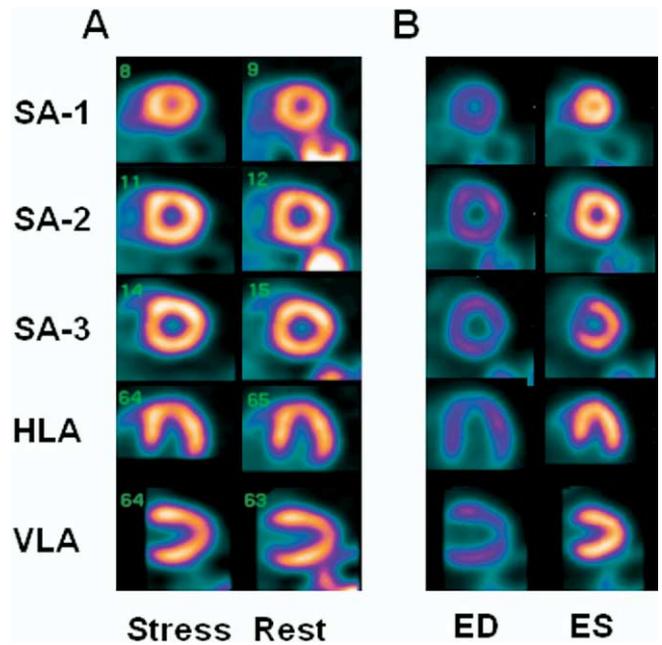
Figure 2 A, Normal stress and rest [82]Rb PET images. B, Resting end-diastolic (ED) and end-systolic (ES) gated images, showing uniformly good contractility.

stress, the patient is injected with the final 50- to 60-mCi [82]Rb dose, for an 8-min dynamic (phasic) acquisition. The total camera acquisition time is approximately 45 min. The need for repositioning, repeating an acquisition, or clinical factors may extend the required time.

For the rest and stress perfusion image reconstruction, we
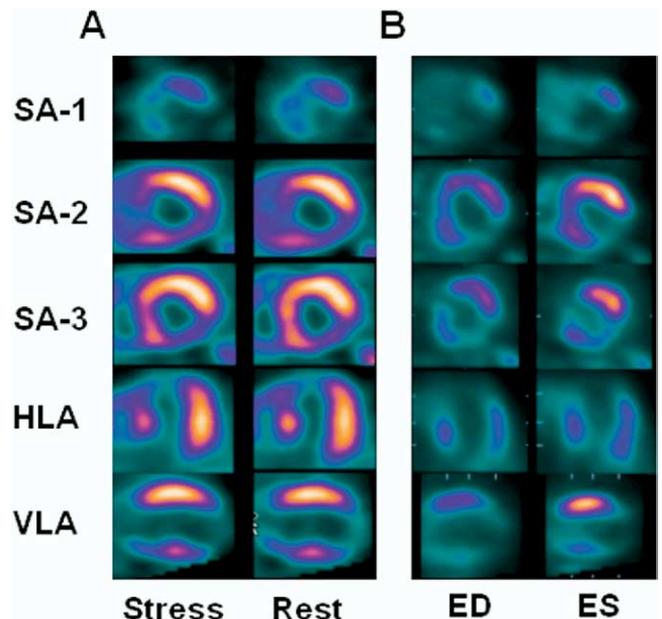
Figure 3 A, Stress and rest of [82]Rb PET images demonstrating severe extensive apical, septal, and inferior scarring and only minimal basal septal ischemia. B, Resting end-diastolic and end-systolic gated images, showing poor or absent contractility in the scarred regions, and poor overall left ventricular function.
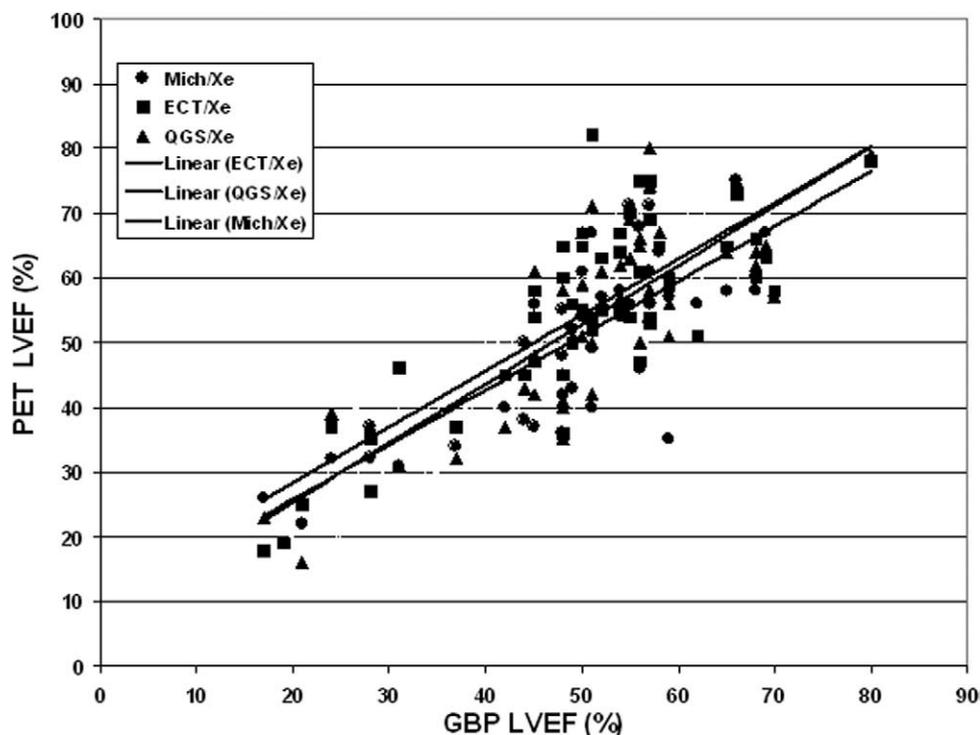
Figure 4 LVEFs obtained from gated ^{82}Rb PET imaging and QGS/Xe, Emory Tool Box (ECT/Xe), and Michigan 4D (MICH/Xe) software, correlated with planar gated blood pool imaging.[236]

have found that filtered back projection with a reconstruction filter and measured attenuation correction produces the best myocardial image uniformity. Iterative reconstruction produced greater regional nonuniformity in normal controls.[43] These results are specific to our PET scanner (AD-VANCE-GE Medical Systems) and should be checked for other scanners. For gated wall motion images, we use iterative reconstruction with segmented attenuation correction to suppress the higher level of noise. The resulting images can be displayed using any of a number of software packages developed for SPECT and adapted for PET.

An important decision is the choice of 2D versus 3D PET imaging, specific for each type of PET scanner. In studies with our bismuth germanate (BGO) crystal scanner, acquisition in 3D mode with high injected doses (50-60 mCi) of ^{82}Rb and immediate acquisition resulted in excessive dead-time and randoms. We obtained good results by delaying acquisition for 5 min after injection, although that defeats the purpose of imaging early in trying to maximize counts. Similar image quality could be obtained with low-dose (20 mCi) ^{82}Rb 3D imaging as with high-dose (50-60 mCi) 2D imaging.[44,45] Our experiments with phantoms showed similar resolution and image quality for 3D and 2D images in lean individuals. In obese individuals, both contrast and image quality were better with 2D imaging. Quantification with 3D imaging should be done with caution, since 3D imaging without proper correction produces significant axial nonuniformity.[46] A clear benefit of 3D imaging with our scanner would be realized if a less expensive low-dose ^{82}Rb generator

were offered. One could then obtain similar results with low-dose 3D imaging as with high dose 2D imaging, at lower cost.

Lutetium orthosilicate (LSO) crystal detector PET scanners (CTI, Knoxville, TN), offer the ability to function in 3D mode at high activities. The cardiac PET laboratory at the Mid America Heart Institute of Kansas City, MO, acquired in quick succession, 2D perfusion and 3D gated imaging at rest and with stress (Table 5). A quantitative comparison[47] between 2D and 3D ^{82}Rb perfusion acquisitions showed the resting images to be identical. 2D and 3D dipyridamole stress images showed significant differences, although follow-up studies showed stress 3D imaging to perform as well as 2D mode imaging in accuracy of perfusion defect detection. Another laboratory observed that compared with a BGO 2D system, an LSO 3D system using a lower 30- to 50-mCi ^{82}Rb dose obtained reduced noise levels, albeit with increased background levels,[48] presumably as the result of a higher randoms level. These observations need to be explored further. Germanium-based 3D scanners also are available (Philips, Cleveland, OH).

With proper image processing, good quality ^{82}Rb PET-gated images can be obtained in the vast majority of patients. Poor gated image quality results from arrhythmia or a slow or fragmented ^{82}Rb injection. We compared visually assessed regional and global left ventricular function from gated ^{82}Rb PET studies to either gated SPECT images or gated planar blood pool images and we demonstrated a 92% agreement in segmental wall motion scores.[49] More recently, we compared the left ventricular ejection fraction (LVEF) calculated with 3
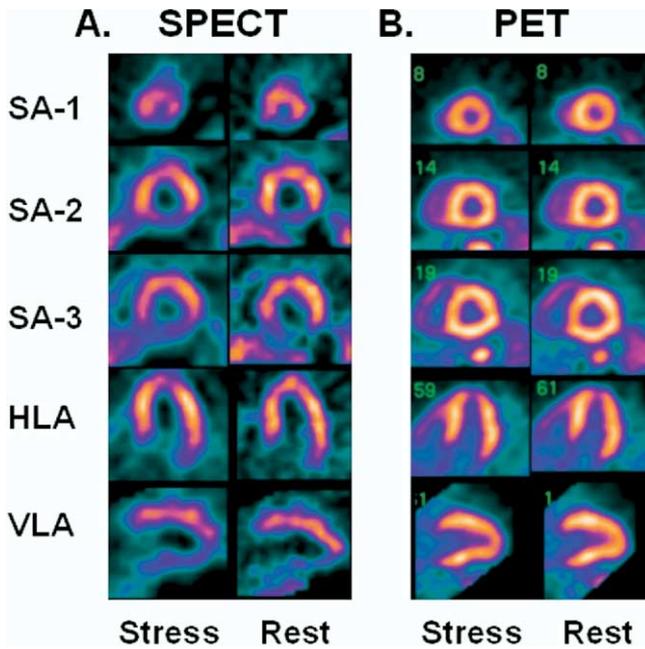
Figure 5 A. Dipyridamole stress and rest ^{99m}Tc sestamibi SPECT images. The stress images show a moderate inferior defect and possible mild anterior defect with mild improvement in the anterior wall and apex at rest. B, The stress and rest PET images showed uniform distribution.

commercial software packages from gated ^{82}Rb PET images to LVEFs obtained from planar gated blood pool images. The results showed all three methods to perform satisfactorily, with correlation coefficients of 0.81 to 0.83[50] (Fig. 4). Another group compared 3D gated ^{82}Rb PET imaging with an LSO system to gated Tc-99 month sestamibi SPECT. The authors found a good correlation ($r = 0.91$) for the LVEFs between the 2 methods.[51] Regional wall motion and LVEFs obtained from ^{13}N ammonia gated PET images also yielded excellent agreement with other wall motion modalities.[52]

The Value of PET for Clinical Imaging

Image Uniformity in PET Imaging

A major challenge for cardiac radionuclide perfusion imaging is nonuniform attenuation of gamma photons in the chest, varying markedly between men and women, and among individuals within each gender. Image uniformity is probably the most important property of cardiac PET perfusion imaging. With coincidence detection, the probability of attenuation for the two gamma photons is uniform along the line between any 2 detectors. This can be measured and corrected. With a conventional gamma camera, resolution deteriorates with distance from the gamma camera, along with attenuation at increasing depth within the subject, which is difficult to model and correct reliably.[53] Although normal maps for SPECT images are nonuniform and different for men and women, the maps with ^{82}Rb PET are uniform and identical for both genders.[54] This is illustrated in Figure 5 for a patient referred for dipyridamole ^{99m}Tc sestamibi SPECT imaging for preoperative risk evaluation. The gated SPECT images showed global hypokinesis. Even though attenuation artifact was suspected, the study could not exclude inferior wall scarring, and possible mild apical and anterior wall ischemia. A short time afterward, stress and rest ^{82}Rb PET images showed uniform distribution. Coronary angiography, performed despite these results, showed normal coronary arteries, with mild diffuse left ventricular dysfunction, probably due to chronic hypertension.

Table 6 lists 8 studies that compared PET myocardial perfusion imaging with angiography, some performed with ^{13}N ammonia and others with ^{82}Rb. Representing a total of 791 patients, they showed a mean 93% sensitivity and 92% specificity for CAD. Table 7 lists studies that compared PET myocardial perfusion imaging with ^{201}Tl SPECT imaging in the same patients. These studies showed higher overall sensitivity, specificity, and accuracy for PET compared with SPECT imaging.

Nondiagnostic or uncertain interpretation of a noninvasive test is one of the factors prompting physicians to recommend further invasive diagnostic studies. In 2748 patients, Patterson and coworkers[55] found a reduction in the number of interpretations classified by 2 experienced physicians as "probably" normal or abnormal, from 37% with ^{201}Tl SPECT, to 21% with ^{82}Rb PET. Regional quantification has been shown to further improve the accuracy of PET perfusion imaging[56,57] with a 99% sensitivity, 83% specificity, and 100% normalcy rate for CAD and a high interobserver agreement of 94% among 3 physicians.[58,59]

During the last 10 to 15 years, both SPECT and PET im-

Table 6 Diagnostic Accuracy of PET Myocardial Perfusion Imaging for CAD

Sensitivity (%)	Specificity (%)	No. Patients	Agent	Author
95	100	50	NH$_3$, ^{82}Rb	Gould et al[224]
94	95	193	^{82}Rb	Demer et al[225]
93	78	202	^{82}Rb	Go et al[226]
97	100	45	NH$_3$	Schelbert et al[227]
93	100	49	NH$_3$	Yonekura et al[228]
98	93	146	^{82}Rb	Williams et al[229]
84	88	81	^{82}Rb	Stewart et al[230]
95	95	25	NH$_3$	Tamaki et al[231]
93	92	791		Average

Table 7 Comparison of PET and SPECT Myocardial Perfusion Imaging for Detection of CAD in the Same Patients

Author	Tracer	Accuracy (%)	Sensitivity (%)	Specificity (%)
Go et al[232] (n = 132)	Rb-82	92	95	82
	T1-201	78	79	76
Stewart et al[233] (n = 81)	Rb-82	85	87	82
	T1-201	78	87	52
Tamaki et al[234] (n = 51)	NH3	98	98	100
	T1-201	98	96	100
Total (n = 264)	PET	91	93	82
	SPECT	81	85	67

aging have undergone significant improvements.[60-65] A recent comparison between Tc-99m sestamibi SPECT and Rb-82 PET myocardial perfusion imaging revealed a significant margin of improvement for CAD detection accuracy with Rb-82 PET compared to SPECT (see Bateman et al[241]). The current literature on the accuracy of PET in comparison with gated attenuation-corrected SPECT is inadequate. Nonetheless, despite ongoing improvements in the accuracy of SPECT, uncertainty remains in many patients even after attenuation correction, with differences in the ability of attenuation correction systems to reduce artifacts.[66]

SPECT imaging in women is challenged by breast attenuation artifact, as well as smaller heart size.[67-69] Williams and coworkers[70] observed a high specificity of stress PET imaging in female patients in relation to coronary angiography. In women who had undergone both stress SPECT and stress PET imaging within a period of 3 months, the SPECT and PET imaging tests had similar high sensitivity, but the specificity for PET was significantly higher than for SPECT. Figure 6 features a 72-year-old female status post heart transplant.
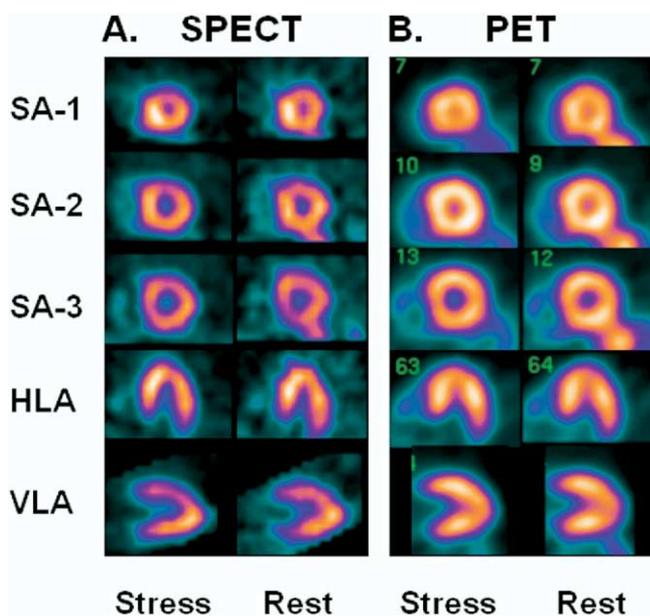
The SPECT images showed a moderate anterior wall defect, with a suggestion of improvement at rest. Even through attenuation artifact was suspected, disease could not be ruled out. The PET imaging study showed normal images. In patients studied with coronary angiography, Patterson and coworkers[71] showed that sensitivity and specificity of CAD detection with PET were equally high for men and women.

An increasing challenge to noninvasive diagnostic imaging is posed by the growing prevalence of moderate and severe obesity in the general population (Table 8). The prevalence of obesity is greater in women, in older individuals, and among African Americans and Hispanic Americans.[72] Obese patients nearly always produce attenuation artifacts on myocardial SPECT perfusion imaging, leading to uncertain results.[73,74] Figure 7 shows SPECT and PET images of a 290-lb, 51-year-old male, with risk factors for CAD. The SPECT attenuation-corrected images show mild to moderate inferior and apical defects which slightly improved on the resting images, accompanied by 1-mm ST depression with nearly maximal exercise. Rb-82 PET images obtained a short time afterward showed a normal distribution. The defects seen on SPECT even after attenuation correction can still be attributed to attenuation.

There are limitations to the ability of PET to image very obese individuals. Most imaging tables are limited to 400- to 450-lb loads. Frequently, the size of the scanner opening is the limiting factor, particularly if it is 60 to 63 cm in diameter. Several currently marketed PET scanners with an opening of 70 cm can be more easily accommodate very large patients.[75]

Imaging in the Pediatric Population

The pediatric population also poses a challenge for diagnostic SPECT imaging. Infants and children can derive benefit from assessment of coronary vessels following switch operations, correction of anomalous coronary arteries (Kawasaki's disease), or in patients with myocardial injuries. Image quality is

Figure 6 A, ^{99m}Tc sestamibi dipyridamole stress and rest SPECT images show a mild-to-moderate anterior wall defect at stress with a suggestion of partial improvement at rest. B, The ^{82}Rb PET imaging study shows normal images.

Table 8 Prevalence of Obesity (BMI >30) in Adults[235]

Year	Men (%)	Women (%)
1960	10.7	15.8
1972	12.1	16.6
1978	12.7	17
1990	20.6	25.9
2000	27.7	34
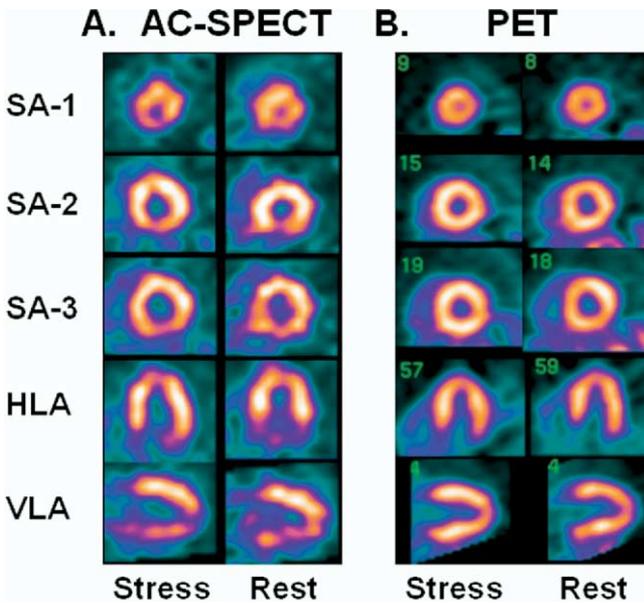
Figure 7 A, Stress and rest attenuation-corrected (AC) ^{99m}Tc sesta-mibi SPECT images of a 290-lb, 51-year-old male. The SPECT image shows mild-to-moderate inferior and apical ischemia and partial scarring. B, The stress and rest PET images showed normal distribution.

limited by poor resolution and low usable activity of ^{201}Tl. ^{99m}Tc sestamibi and ^{99m}Tc tetrofosmin images are compromised by high liver activity in close proximity to the small heart. We have found the results of PET ^{82}Rb myocardial perfusion imaging in infants and in small children to be excellent. The short half-life of ^{82}Rb or ^{13}N ammonia allows sufficiently high doses of tracer to be delivered to achieve good quality images with low radiation exposure to the child.

Prognostic Value of Myocardial PET Imaging

Given the proven value of PET myocardial perfusion imaging in the diagnosis of CAD, it is expected that the prognostic value of gated PET is also high, similar to SPECT imaging. In 153 patients studied with ^{82}Rb PET imaging, Yoshinaga and coworkers showed 94% event-free survival during a 3-year period in patients with normal PET scans, compared with 62% with mild defects, 58% with moderate defects, and 45% survival with severe defects.[76] VanTosh and coworkers[77] showed that a normal stress PET study in women with chest pain and significant cardiac risk factors predicts a very low cardiac event rate.

Detection of Diffuse and Early Disease

PET imaging appears to be useful in the diagnosis and prognostication at an early stage in disease and in the measurement of the response to dietary and lifestyle changes and antilipid drug therapy.[78,79] Merhige and coworkers[80] studied 128 patients with CAD with stress and rest ^{82}Rb PET. After aggressive lipid-lowering therapy, 80 patients demonstrated improvement in myocardial perfusion, 64 patients showed

no change, and 34 showed progression of CAD despite treatment at a mean follow-up of 1.5 years. Then, 7.5 months after the second scan, coronary events had occurred in 3.3%, 10.9%, and 17.7% of patients, respectively. Thus, PET perfusion imaging identified 26% of patients with progressive CAD, despite lipid lowering therapy, at a high-risk of subsequent hard coronary events.

Base to Apex Flow Gradient Quantification

Invasive studies with Doppler flow and pressure probes have demonstrated a continuous gradient between the proximal and distal portions of coronary arteries with diffuse, though nonobstructive disease, resulting in a gradient in flow reserve.[82] In such patients, once attenuation correction has been successfully applied, Gould and coworkers demonstrated with PET a graded, longitudinal, base-to-apex myocardial perfusion gradient significantly different from normal control subjects (Fig. 8).[82] This observation was confirmed by Pampaloni and coworkers.[83] An abnormal base-to-apex perfusion gradient observed during vasodilator stress suggests the presence of early or preclinical CAD.
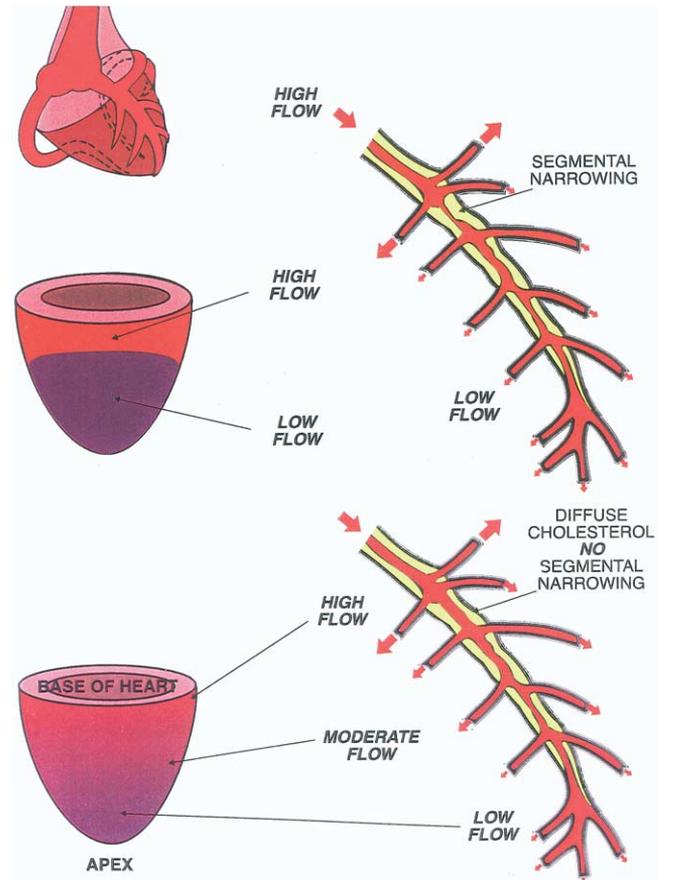
Figure 8 Schema of a longitudinal base-to-apex myocardial perfusion abnormality caused by diffuse coronary artery narrowing compared with segmental perfusion defects caused by localized stenosis. (Reproduced with permission from Gould et al.[82])

Table 9 Clinical Applications of Coronary Flow Reserve Quantification

1. Verification of efficacy of pharmacological vasodilation
2. Detection of global/diffuse disease
3. Evaluation of extent of multivessel disease
4. Evaluation of significance of individual vessel lesions
5. Detection of coronary steal syndrome-collaterals
6. Evaluation of endothelial function
7. Monitoring therapy

Quantification of Myocardial Blood Flow

The noninvasive quantification of myocardial blood flow and coronary flow reserve is one of the most potentially useful but as yet clinically unrealized applications of myocardial PET imaging. Formal quantification of blood flow usually requires a multi-frame (50 frames or so) dynamic PET acquisition. Myocardial and blood-pool activity curves are generated and corrected for decay, partial volume effect, and tissue cross-talk. A compartmental model is then applied to solve for blood flow.

The rapid equilibration of ^{15}O water between plasma, interstitial space, and intracellular water allows the use of a simple 1-compartment model,[84] making this tracer a favorite in scientific studies of quantitative myocardial perfusion. ^{15}O water is not a very useful clinical perfusion imaging agent because of its poor image quality and a requirement for a cyclotron. ^{13}N ammonia has been used for blood flow measurements in many pioneering studies of myocardial vascular pathophysiology.[85] With the use of a 2-compartmental model, satisfactory reproducibility and accuracy are obtainable.[86,87] Quantification of blood flow with ^{82}Rb is possible as well. Because of its 75-s half-life, myocardial and blood pool time-activity curves are noisy. Compartmental analysis of ^{82}Rb in humans has yielded a fair reproducibility in our laboratory ($r = 0.83$).[88] Lin and coworkers demonstrated that with specialized wavelet-based noise reduction methods, the correlation between ^{82}Rb flow with ^{15}O water flow was excellent ($r = 0.94$).[89]

Limitations of compartmental modeling include the need for a multiframe dynamic acquisition, requirement for high expertise, and the fact that it is time-consuming. It is likely that standardized acquisition protocols and commercial development of analysis software will make this important PET capability accessible for routine use.

It is possible to estimate blood flow and coronary flow reserve using methods which, although lacking the rigor of compartmental analysis, offer greater simplicity and ease of use. The simplest approach uses the ratio of ^{82}Rb uptake during stress and during rest after normalization for injected activity. The uptake ratio reflects coronary flow reserve, although it ignores the effects of cardiac output on the plasma tracer activity and decreasing extraction fraction of ^{82}Rb during hyperemia. The stress/rest ^{82}Rb uptake ratio has been used successfully as an index of blood flow response to stress the presence of left ventricular hypertrophy and in the detection of coronary steal syndrome.[90-92]

A compromise alternative proposed by Yoshida and co-

workers[93] corrects the uptake of ^{82}Rb or ^{13}N ammonia by the summed blood pool activity and by the relation between the extraction fraction and blood flow obtained from animal experiments.[94,95] This approach (simple model) was validated in animal experiments. We have adapted this method for human studies. A comparison of the simple model with the compartmental model yielded a fair correlation ($r = 0.72$, $P < 0.001$), and excellent reproducibility ($r = 0.97$), less susceptible to noise than the compartmental method.[96] Using a similar method of measuring ^{82}Rb retention, DeKemp and coworkers showed a good reproducibility and good correlation with microsphere flow measurements ($r = 0.74$; $P = 0.001$) in animal studies.[97]

Clinical Applications of Myocardial Blood Flow and Coronary Flow Reserve

Some clinical applications of coronary flow reserve (CFR) are listed in Table 9. The first application is quality control to verify the global response to vasodilator stress. A normal flow reserve (greater than 2.0 in our normal population), provides assurance that the stress test was adequate. In patients with decreased flow reserve, ie, patients who ingested some caffeine, those who have small vessel disease because of hypertension or diabetes or endothelial dysfunction because of hyperlipidemia or diabetes,[98,99] or patients with end-stage liver disease,[100,101] the sensitivity of conventional imaging to detect epicardial coronary disease may be limited. In the absence of flow reserve quantification, the adequacy of response to pharmacological stress is unknown.[102]

Another important application is to help detect extensive epicardial disease in a high-risk patient with normal or minimally abnormal stress and rest images due to "balanced ischemia." Figure 9 shows stress and rest images of a 70-year-old male with multiple risk factors for CAD and mild chest pain.
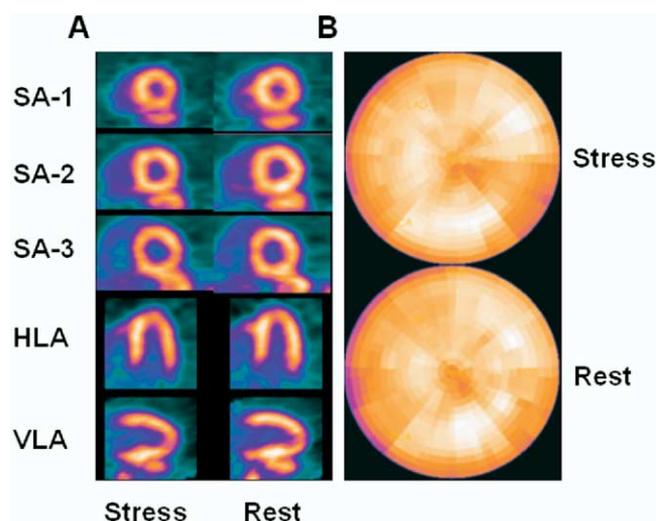
Figure 9 Tomographic slices (A) and the polar maps (B) of stress and rest ^{82}Rb PET images of a 70-year-old male with multiple risk factors for CAD and mild chest pain. The images suggest only minimal apical and inferolateral ischemia. The CFR was 1.3, indicating severe diffuse disease.

During dipyridamole stress, the ECG response was negative, and the stress ^{82}Rb PET images showed only minimal apical and inferolateral ischemia. This would not necessarily be a patient for invasive evaluation, were it not for the fact that the global CFR was only 1.3 (normal CFR >2.0). The patient's angiogram showed 3-vessel disease, which was deemed most severe in the OM1 branch of the left circumflex artery. Quantification of coronary flow reserve has recently been shown to improve differenciation between 3-vessel and 1-vessel disease. Flow reserve quantification thus helps define the full extent of multi-vessel disease,[103] by assessing disease severity not only in the abnormal segments but also in the "normal" segments, when these "normal" segments are used for normalization of stress and rest images.

Coronary arteriography is considered the "gold standard" for evaluating the severity of coronary stenosis. Muzik and coworkers found a high diagnostic accuracy and sensitivity using absolute ^{13}N ammonia blood flow for the detection of coronary disease. In patients with a low probability of CAD, the specificity was also high, whereas an abnormal flow reserve in regions with angiographically normal territories in patients with CAD elsewhere was postulated to represent early functional vascular abnormality.[104] Because the resistance to blood flow through a stenotic lesion depends on a number of lesion characteristics, the physiologic significance of coronary lesions of intermediate severity often is difficult to determine from angiography alone.[105-108] Multiple factors other than lesion diameter influence the measured coronary flow reserve, including the heart rate, resting blood flow, the left-ventricular end-diastolic pressure, contractility, and the magnitude of dipyridamole-induced hyperemia,[109-112] Nevertheless, there is a role for the accurate assessment of the physiologic severity of coronary stenoses as a more objective determination of medical versus mechanical treatment of coronary artery stenosis and for monitoring of the results of their treatment, since clinical tools, such as chest pain, are poorly related to stenosis severity.

Another application of occasional usefulness in intervention is the assessment of collaterals in diseased regions. It is axiomatic that blood flow in diseased arteries does not increase to the same degree as in normal vessels. In multivessel disease, in regions supplied by collaterals, blood flow may actually decrease with stress, demonstrating "coronary steal," which can be detected by quantification of regional blood flow.[113-115] Knowledge of such collaterals, which can't always be seen angiographically, can help in the planning of high-risk intervention procedures.

Another application is the monitoring of the progression or possible regression of diffuse disease in atherosclerosis, hypertension, diabetes, hyperlipidemia, and posttransplant vasculopathy.[116-118] The patient shown in Figure 9 declined CABG and allowed the revascularization of only the OM1, the most severely diseased vessel. The patient was placed on a rigorous antilipid regimen with diet and medication. One year later, the PET study was repeated. The study did not show any focal abnormality, and the global CFR was 2.2 (normal), and at 2 years, the CFR was 2.9, demonstrating reversibility of the hemodynamic effects of CAD with diet and antilipid medication alone, a phenomenon documented in the literature.[119-121]

Detection of Early Disease

Decreased CFR has been found even in the absence of coronary stenoses, in normal-appearing vessels in patients with coronary disease in other vessels.[122-124] The presence of even mild, nonobstructive coronary disease was found to be predictive of progression to clinically significant disease in 6 years.[125] Quantitative PET offers a sensitive tool to detect early disease in high risk asymptomatic individuals with family history of CAD.[127] CFR has been shown to be decreased in hypertrophic disease states,[127] in poorly controlled diabetes or hyperlipidemia.[128-130] Glycemic control and reduction of serum lipids through low-fat diet, exercise and antilipid drugs have been shown to lead to improvements in CFR.[131,132]

Cold Pressor Stress Testing. The vascular endothelium plays an important role in the regulation of circulatory function and in the structural and functional integrity of the vascular wall.[133] Intracoronary acetylcholine normally causes endothelial release of nitric oxide (NO) and vasodilation. In the presence of endothelial disease, acetylcholine produces lack of vasodilation, or even vasoconstriction. Abnormal endothelium-dependent coronary vasomotion has been found to be an independent predictor of coronary artery disease and of coronary events.[134-136] Normal response has been restored after cholesterol lowering and antioxidant therapy.[137]

Endothelial function also can be studied with flow-dependent vasodilation in response to cold-pressor testing (CPT).[138] CPT consists of immersing one hand in ice or ice water for 60 s before the injection of a flow tracer and for 60 s after the injection. CPT results in sympathetic stimulation[139] and alpha-adrenergic mediated vasoconstriction of vascular smooth muscles, which is, under normal conditions, offset by flow-mediated vasodilation and a possible direct adrenergic-induced endothelium-dependent vasodilator response.[140] In the presence of endothelial disease or atherosclerosis, the vasoconstrictor component is left unopposed.[141,142] Changes in luminal area of the epicardial vessels during CPT correlate with changes in coronary blood flow, demonstrating that flow-dependent vasodilation can be studied with measurements of coronary blood flow.[143,144] A 30% to 40% increase in blood flow is considered a normal response to CPT. Despite angiographically normal coronary arteries, a diminished or even paradoxically decreased endothelium-dependent flow response may result in a mismatch between demand and supply, that has been related to myocardial ischemia during daily life.[145-147] An example is given by a 58-year-old female with hyperlipidemia and chest pain, who was initially diagnosed with a distal LAD artery occlusion, which was treated with a stent. After several years of doing well, the patient presented with atypical chest pains at night and in cold weather. An angiogram showed no obstructive disease. The patient underwent serial imaging at rest, CPT, and adenosine stress testing with Rb-82 PET
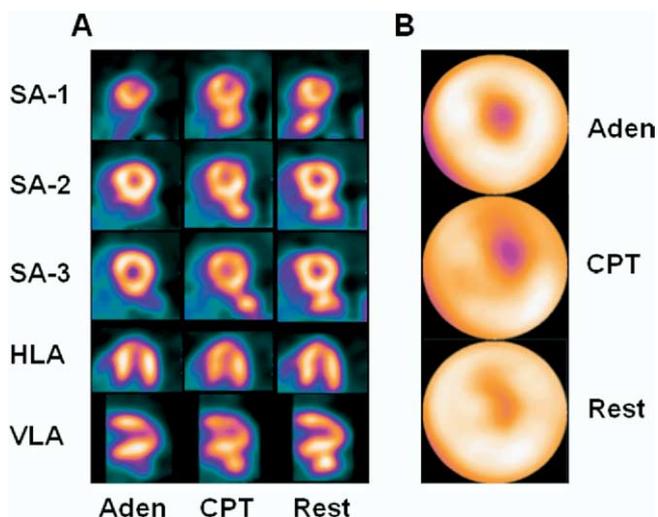
Figure 10 [82]Rb PET tomographic images (A) and polar maps (B) of adenosine stress, CPT, and resting images of a 58-year-old female with atypical chest pains at night and in cold weather but no obstructive coronary disease. Resting perfusion is normal. The adenosine stress images show mild anteroapical hypoperfusion. The cold-pressor perfusion images show moderate anteroapical and extensive mild anterior, anterolateral, and septal hypopoperfusion.

imaging. The results are shown in Figure 10. The resting images are normal. The adenosine stress images show mild anteroapical hypoperfusion suggestive of a base-to-apex flow gradient, as proposed in Figure 8. The cold-pressor images show moderate anteroapical and extensive mild anterior, anterolateral, and septal hypopoperfusion accompanied by her usual chest pain. The patient was given a calcium channel blocker, and more aggressive antilipid therapy with complete relief of symptoms.

Abnormal responses to CPT have been found in early coronary artery disease,[148] hyperlipidemia,[149,150] insulin resistance,[151] diabetes,[152,153] elevated CRP levels,[154] the metabolic syndrome,[155] elevated leptin levels in obese individuals,[156] and smoking.[157,158] Endothelial dysfunction is reversible with insulin-sensitizing drugs in the case of insulin resistance, improved glycemic control or ACE inhibitors in diabetes, L-arginine, citric acid or smoking cessation in smokers, and antilipid therapy in patients with elevated serum lipids.[159-162] Abnormal CPT results have been associated with menopause,[162] that can be reversed by long-term hormone replacement therapy.[163]

The response to CPT is more dramatic compared with the minimal changes in angiographic CAD lesion characteristics or lumen diameter[164] and tends to be more sensitive than the response to hyperemia (dipyridamole or adenosine).[165] The fact that some patients with risk factors have a normal response to CPT, whereas others have an abnormal response, or that some "normal" subjects may have an abnormal response,[166] attest to the variability of the susceptibility of the individual. Of relevance is the observation that only 50% of the total attributable risk burden for CAD can be related to conventional risk factors,[167,168] warranting an alternative determination of risk

for the development of atherosclerosis. Noninvasive CPT can serve as an early marker of endothelial dysfunction, and development of atherosclerosis, that is susceptible to reversibility with diet and medication.[169]

Is Myocardial PET Perfusion Imaging Cost-Effective?

The use of PET perfusion imaging has been shown to be cost-effective through its enhanced diagnostic power. The results of an analysis by Gould and coworkers[170-172] are shown in Figure 11. The most expensive diagnostic approach is that of coronary angiography in all patients with a pretest probability of less than 70%. In patients with a greater than 70% likelihood of disease, angiography is more cost-effective for diagnosis. Both SPECT and PET achieve a savings compared with performing angiography, due to deceased referral for unnecessary coronary catheterization. PET achieves a savings compared with SPECT for patients with a probability of disease between 0 and 60. If only half of patients with an abnormal noninvasive test undergo angiography, then the cost savings of PET is even greater. A cost analysis by Patterson and coworkers[173] came to similar conclusions.

Merhige[174] studied what actually happens when PET imaging is introduced into clinical practice. 102 patients studied with stress-rest [82]Rb PET imaging were identified, with a mean pretest probability for CAD of 37% were compared with 102 matched patients tested with SPECT. After a follow-up of 12 months, the use of PET led to a reduction in the false positive rate resulting in a reduction in angiographies. While there was no significant change in the rate of angioplasties, there was a reduction in the number of bypass operations. The diagnostic cost per patient was similar for SPECT and PET, despite higher cost of PET per study, due to lower referral for further diagnostic studies. The therapeutic
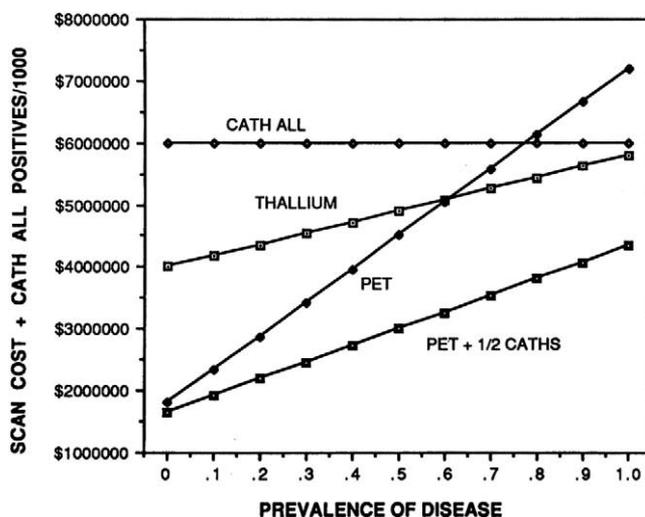
Figure 11 Comparative costs of ^{201}Tl SPECT, [82]Rb PET, and coronary angiography as a function of disease prevalence. (Reprinted by permission of the Society of Nuclear Medicine.[238])

cost per patient was lower with PET, attributable to a reduction in the number of bypass operations, as predicted by Patterson and coworkers.[175]

Myocardial Viability

Why PET Viability Imaging Matters

Viability imaging is reviewed separately in this seminar. The consideration of myocardial viability is important in a patient with impaired left ventricular function because of coronary artery disease with a possibility of revascularization. Flow measurements in these dysfunctional regions by SPECT or PET perfusion imaging, particularly those with mild-to-moderate flow reduction do not by themselves distinguish between regions with potentially reversible dysfunction and regions with irreversible dysfunction.[176] Combined metabolic and perfusion PET imaging offers diagnostic power in the prediction of myocardial functional recovery of viable myocardium.

It also has high prognostic power in predicting symptomatic improvement in patients with congestive heart failure[177] and predicting high level of cardiac events in patients with poor left ventricular function in the presence of significant areas of perfusion-metabolism mismatch treated medically, and lower event rate in patients undergoing revascularization.[178-183]

The clinical value of cardiac FDG-PET imaging in the assessment of myocardial viability in combination with perfusion imaging was demonstrated more than 18 years ago.[184] In direct comparison between thallium-201 SPECT or ^{99m}Tc Sestamibi with FDG imaging in the same patients with very poor left ventricular function, FDG-PET imaging showed incremental benefit over thalium-201 stress-redistribution /reinjection or ^{99m}Tc sestamibi SPECT imaging in predicting functional recovery, while in patients with relatively preserved left ventricular function, the predictive value was similar.[185,186] PET viability imaging also has been successfully applied in infants and children with high accuracy, similar to that seen in adults.[187]

In our protocol, the patient undergoes resting perfusion imaging with ^{82}Rb and, whenever possible, pharmacologic stress ^{82}Rb perfusion imaging. This is followed by FDG-PET imaging, which begins with glucose loading and supplementary insulin.[188] The patient is injected with FDG. After a 1-h rest, the patient then undergoes emission PET imaging, along with a transmission scan.

Because ^{82}Rb is an analog of ^{201}Tl, it is not surprising that ^{82}Rb often shows reversible stress-rest defect, whereas ^{99m}Tc sestamibi or ^{99m}Tc tetrofosmin SPECT studies show extensive fixed defects.[189] Nevertheless, FDG-PET imaging frequently shows additional viability in patients with fixed ^{82}Rb perfusion defects or in patients with only partial stress-inducible reversibility. An example is a 49-year-old male with a history of myocardial infarction, very poor left ventricular function, and congestive heart failure. Exercise stress ^{99m}Tc MIBI images (Fig. 12) showed severe apical, anterior, lateral, and inferior defects, with no improvement on the rest images.
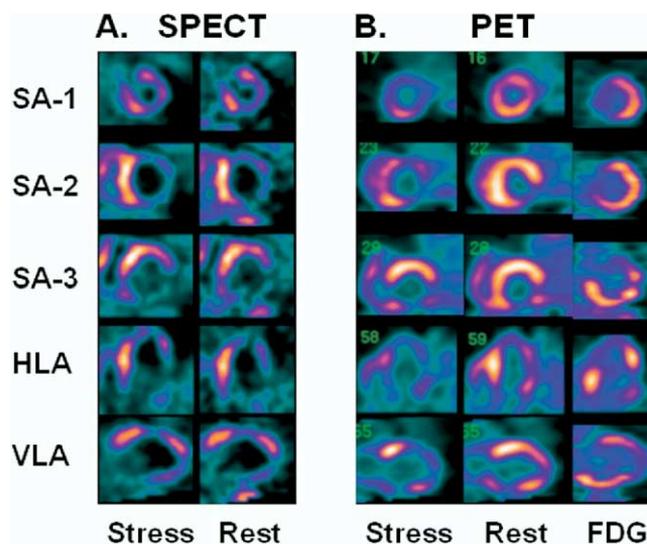
Figure 12 A, ^{99m}Tc sestamibi (MIBI) exercise stress and rest images in a 49-year-old male with known CAD and congestive heart failure. The MIBI images show severe apical, anterior, lateral, and inferior defects with no improvement on the resting images. B, The dipyridamole stress ^{82}Rb images show severe apical, anterior, lateral and inferior-basal defects, and a moderate-to-severe septal defect. The resting ^{82}Rb images show marked anterior, septal and anterolateral improvement, and mid-inferior improvement. The FDG-PET images showed preserved or increased activity in the anterolateral, lateral, inferior and inferior-basal walls, demonstrating a classical mismatch pattern in these regions.

Dipyridamole stress ^{82}Rb images showed severe apical, anterior, lateral, and inferior defects, and a moderate to severe septal defect. The resting images, however, showed marked anterior, septal and anterolateral improvement, and inferior improvement. The extent of stress-inducible ischemia was at least 50% of the myocardium. In addition, the FDG PET images showed preserved or increased activity in the anterolateral, lateral, inferior and posterior walls, demonstrating a classical mismatch pattern in these regions, occupying at least 50% of the myocardium. About 75% of the myocardial mass showed either stress-inducible ischemia or hibernation, including most of the regions considered scarred by MIBI SPECT imaging. In some instances, it is not necessary to proceed with FDG PET viability imaging, if the stress and rest ^{82}Rb PET imaging provides evidence of ischemia, rather than scarring.

Studies of PET Perfusion Tracer Kinetics for Viability

Because ^{82}Rb is an analog of ^{201}Tl, an attempt was made to analyze myocardial kinetics with ^{82}Rb. Despite the short half-life of ^{82}Rb, animal studies showed that acutely injured, post-ischemic myocardium that eventually proved to be viable showed retention of ^{82}Rb, whereas myocardium, which proved to be necrotic, showed washout of ^{82}Rb.[190] This was supported by clinical studies that measured the washout rate between 1 to 2 min after injection versus 4 to 6 min afterward (Fig. 13) and compared uptake and retention of ^{82}Rb in com-
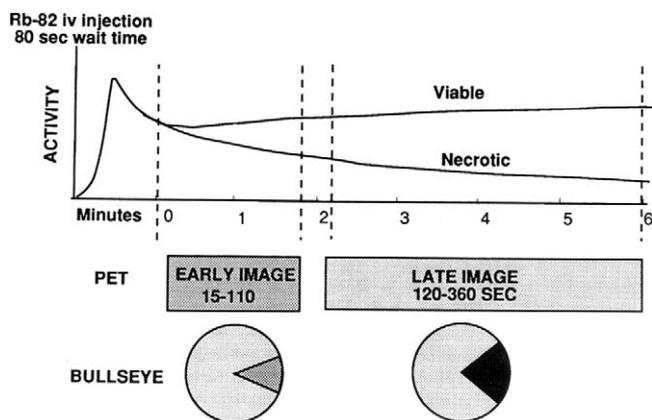
Figure 13 Schematic of the imaging protocol utilizing washout or retention of Rb-82 for assessing myocardial viability. (Reprinted by permission of the Society of Nuclear Medicine.[239])

parison to FDG-PET imaging studies.[191,192] Another study found a significant difference in [82]Rb kinetics between metabolically active and irreversibly injured myocardium.[193] We found a greater [82]Rb washout rate with increasing severity of defects, regardless of the FDG uptake.[194] This issue remains open to further studies.

Beanlands and coworkers[195] studied the ability of ^{13}N ammonia kinetic modeling to calculate viability and compared the results with ^{18}F FDG uptake. Flow and the volume of distribution were both reduced in the hypoperfused regions of patients with scar, whereas partially preserved flow and volume of distribution were seen in regions with viability. The sensitivity and specificity of this combination were 100% and 90%, respectively. These interesting results deserve further studies.

Technical Problems Encountered With Cardiac PET Imaging

The vast majority of patients tolerate PET imaging well. Occasional patients do feel claustrophobic. Patients should be offered sedation in that event. Frequently, a thorough explanation of the procedure, providing reassurance, soothing or favorite music, and close supervision can overcome this difficulty without medication.

Myocardial PET imaging is subject to artifacts. A faulty detector block can cause a major streak and defect artifact. Recognition and checking the PET blank study aids in diagnosing the problem. The assumption of successful PET attenuation correction is that the transmission scan reflects the true position of the heart, diaphragm and adjacent structures. Significant displacement of the average position of the heart due to hyperventilation during stress or a change in respiratory pattern after falling asleep will violate that assumption and leads to artifact.

Our recent work with 178 patients studied with dipyridamole stress and rest [82]Rb PET imaging[196] showed that prevalence of noticeable vertical heart movement of more than 10 mm was 6% in an unselected group of 100 patients, 17% in a subset of 78 asymptomatic patients, and 14% in a subset of 27 patients at low risk of CAD. Despite that, there was no significant increase in frequency of PET scan defects with large or small heart drop in any of patient subgroups, including in the group with low probability of CAD. Fortunately motion does not always lead to artifactual findings, but should be suspected in cases of basal anterolateral, anteroseptal or lateral defects in the presence of excessive displacement.

Analysis of artifacts in PET perfusion images due to transmission-emission misregistration was recently published by Loghin and coworkers,[197] who performed 1177 studies with either [82]Rb or ^{13}N ammonia, while varying the order of transmission and emission scans. They found that 21% of subjects had artifactual defects due to transmission-emission misregistration. Misregistration defects were predicted by horizontal plane misregistration, which was predicted by diaphragm displacement between rest and dipyridamole stress images, a greater body mass index, and small heart size. Misregistration was greatest with transmission scans performed early in the imaging protocol. This was predictably greater in obese individuals, suggesting delayed displacement of the diaphragm after positioning due to pressure from abdominal contents. By shifting the emission images to match the transmission scan during postprocessing, the quantitative severity and size of defects was significantly decreased.

This problem needs appropriate software to display superimposed emission and transmission scans, timely visual or automatic recognition of misregistration movement, both in plane and between transaxial planes, and taking corrective measures. When feasible, a separate transmission scan with each of the resting and stress studies used in some laboratories is a useful step (Table 5). In our protocol (Table 4), we perform the transmission scan after the resting scans, just before the pharmacological stress, thus close in time to both rest and stress imaging. This may account for the relatively lower frequency of displacement misregistration artifact in our studies.[198]

Impact of PET-Computed Tomography (CT)

Combined PET and CT imaging in a single combined PET-CT unit has become the preferred approach for PET imaging in oncology. Approximately 80% new PET units installed in 2003 were PET-CT units (GE Medical Systems, personal communication, 2004). Table 10 summarizes the potential benefits of PET-CT in cardiac imaging. First, the scout CT scan can, in a few seconds, check the proper positioning of the patient. The CT transmission scan lasting 15 to 30 s reduces imaging time. The time savings is not only the time needed for the pin-source transmission scan, but because the CT transmission scan is relatively free of noise, it reduces the amount of noise in the attenuation-corrected emission scan, thereby reducing the length of time required for the emission scan itself. One group reported saving 12

Table 10 Value of PET-CT

1. Positioning
2. Attenuation correction
3. Calcium scoring
4. Coronary angiography
5. Contrast ventriculography

min per study after switching from a dedicated PET system to a PET-CT system.[199] Because 30 to 35 min are required for the entire study, with possibly 45 minutes for the more difficult patients,[200] throughput should be enhanced.

PET-CT imaging holds both challenges and solutions for the attenuation correction problem. It is possible to repeat the CT transmission scan separately for both rest and stress images.[201] The CT transmission and PET emission scans can be easily displayed using existing display software. The CT transmission map can be potentially moved to provide more reliable attenuation correction.

CT attenuation correction also is more susceptible to artifacts produced by metallic implants or pacemakers, than pin source-produced attenuation maps. A very short scanning time for the CT attenuation map may under-sample the position of the heart and diaphragm, due to cardiac contraction, and respiratory movement,[202] seen frequently in whole body PET imaging for oncology purposes.[203] The transmission scan needs to be obtained over a sufficient number of respiratory and cardiac cycles, to match the average position of the heart during the emission scan at rest and again during stress.[204] The radiograph tube current used for the transmission scan needs to be low, to minimize radiation exposure. Such an approach has been taken at the Brigham and Women's Medical Center (Table 11). The most optimal protocol for PET-CT has not yet been determined, due to the limited experience with PET-CT imaging of the heart. Respiratory gating of the CT as well as the PET images offers the potential for a closer emission-transmission match.[205-207] It is hoped that PET camera manufacturers will address this important need.

Another potential application of PET-CT is the possibility of obtaining coronary calcium scores at the same imaging session as the PET scan, which is feasible with an 8- or 16-slice multidetector CT scanner. Calcium scoring requires a higher current from the CT radiograph tube than the transmission scan, resulting in higher patient radiation exposure, but still lower than for CT diagnostic imaging. The clinical value of coronary calcium scoring is at this time still an open question in clinical practice. In patients with risk factors but few symptoms being screened for CAD, calcium scoring can add specificity when the calcium score is low and the perfusion results are equivocal or abnormal due to endothelial dysfunction. The calcium score can add sensitivity in the detection of preclinical CAD, even in the presence of normal myocardial perfusion. Facta and coworkers[208] found that the presence of calcium is associated with mild functional alteration of coronary circulation in apparently healthy individuals, whereas in type 2 diabetic patients, coronary vasomotion abnormalities were independent of epicardial calcifications.

By contrast, Prior and coworkers[209] found that the flow response to CPT or adenosine did not correlate with calcium scores. Glass and coworkers[210] found that the presence, location, and severity of myocardial perfusion defects or angiographic lesions did not correlate with global calcium scores. Thus, regional coronary disease and calcium deposition provide different information. Their interaction and significance needs to be explored.

An intriguing possibility is the potential value of CT coronary angiography performed together with PET rest and stress and/or viability imaging in selected patients. Multislice (16 slices or greater) CT scans have been found to have sufficient temporal resolution to image, with intravenous contrast, coronary arteries with a diameter or 1.5 mm or greater, with a reported sensitivity for 50% or greater coronary lesions of 86% to 92%, a specificity of 93% to 99%, and accuracy of 93% compared with invasive coronary angiography.[211,212] There are limitations in visualizing lesions in the smallest distal vessels, and in the presence of heavy calcifications. The latter limitation can be overcome with the aid of the PET perfusion results.[213]

It is conceivable that patients with known or suspected disease could be studied with sequential stress-rest perfusion imaging and CT angiography and ventriculography, allowing acquisitions of superimposed images of both coronary anatomy, perfusion, wall motion, and viability.[214] This complete set of spatially mapped information could add precision and ease to decision-making for interventions in multivessel disease intervention planning, or in patients with physiologically abnormal perfusion but anatomically normal coronary arteries. This proposition still needs to be tested in clinical studies.

Future Prospects

The extensive infrastructure of PET scanners, availability of perfusion and viability tracers and reimbursement have set the stage for more widespread use of PET for indications shown to be of benefit. In the meantime, there have been several major paradigm shifts in the understanding and management of coronary disease, in which PET imaging of the heart is well suited to play a role. One is the shift in emphasis from the assessment of structural to functional alterations. With quantification of myocardial blood flow, PET can detect

Table 11 Imaging Protocol for [82]Rb PET Imaging With a PET–CT Scanner[234]

Procedure	Time
Positioning (Scout)	1 min
CT transmission scan	1 min
Rest gated imaging	8 min
Rest perfusion imaging	8 min
Pharmacological stress	7 min
CT transmission scan	
Stress imaging	8 min
Total duration	33 min

early endothelial disease in the absence of obstructive disease, which is predictive of future development of disease, even in patients that lack classical risk factors, and which can be reversed by lifestyle, dietary, and pharmacologic interventions. Thus, the study of endothelial dysfunction is suggested to be a key to the early diagnosis and control of early coronary disease. Another unique feature of PET is the ability to image as yet nonroutine tracers labeled with isotopes like ^{18}F, ^{11}C, and [13]N. Finally, a major paradigm shift is offered by the intriguing potential of combined multimodality imaging, represented by PET-CT imaging. The growing PET infrastructure is allowing PET imaging to become a tool in the noninvasive assessment of in vivo cellular metabolism, receptor function and gene expression, which hold great potential in applications beyond perfusion and glucose metabolism discussed in this review.

Acknowledgments

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