Assessment of Myocardial Perfusion by Positron Emission Tomography

Markus Schwaiger, MD and Otto Muzik, PhD

Positron emission tomography (PET) represents an advanced imaging technology for the noninvasive evaluation of regional myocardial blood flow. Several blood flow tracers are available, including cyclotron-produced radiopharmaceuticals such as [^{15}O]H_2O and [^{13}N]NH_3 and generator-produced rubidium-82 ([^{82}Rb]-) and copper-62 ([^{62}Cu]-) pyruvaldehyde-*bis*-(*N*-4-methylthiosemicarbazone) (PTSM). ^{82}Rb and [^{13}N]NH_3 are the most commonly employed tracers for the qualitative evaluation of regional myocardial perfusion. Their use allows the accurate detection of coronary artery disease in combination with pharmacologic stress. Initial comparative studies with thallium-201 (^{201}Tl) single-photon emission computed tomography (SPECT) have shown that PET has a higher diagnostic accuracy.

Beyond improved diagnostic performance, the quantitative flow measurements provided by PET represent an important advance in nuclear cardiology. The radiopharmaceuticals [^{15}O]H_2O and [^{13}N]NH_3 have been applied for the noninvasive determination of regional coronary reserve. Quantification of blood flow based on tracer kinetic modeling yields blood flow values in close agreement with determinations provided by invasive procedures. The noninvasive quantification of blood flow provides a useful research and clinical tool for the objective assessment of therapeutic interventions as well as pathophysiologic alterations of regional myocardial blood flow in various cardiac diseases.

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From the University of Michigan Medical Center, Department of Internal Medicine, Division of Nuclear Medicine, Ann Arbor, Michigan.

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Address for reprints: Markus Schwaiger, MD, University of Michigan Medical Center, 1500 E. Medical Center Drive, UH B1 G505, Box 0028, Ann Arbor, Michigan 48109-0028.

Positron emission tomography (PET) technology has matured over recent years to become an established imaging modality for the noninvasive characterization of cardiac disease. Significant advances in scintigraphic data acquisition with multi-slice PET instrumentation allow three-dimensional determination of regional tissue tracer concentration. Furthermore, an abundance of radiopharmaceuticals labeled with carbon-11 (^{11}C), nitrogen-13 (^{13}N), oxygen-15 (^{15}O), or fluorine-18 (^{18}F) provide sophisticated delineation of specific tissue functions. The temporal definition of tissue tracer kinetics and subsequent analysis with mathematical models enable quantitative measurements of physiologic processes such as blood flow and metabolic rates.

Although coronary angiography is considered to be the "gold standard" for the characterization of coronary artery disease (CAD), data increasingly support the importance of noninvasively assessing the functional definition of the severity and extent of the disease process.[1] Regional measurements such as absolute or relative coronary reserve have been shown to provide a sensitive marker for the functional significance of coronary artery stenoses. Such measurements represent functional correlates to the anatomic definition of vascular abnormalities occurring in CAD. Although these measurements can be obtained invasively by several methods, at the present time PET represents the only noninvasive approach that accurately quantifies regional myocardial perfusion.[2,3]

This review addresses the clinical role of blood flow imaging with PET for the detection of CAD, using qualitative evaluation of regional tracer distribution. Additionally, current methods of quantification of regional myocardial blood flow under various physiologic conditions are compared.

RADIOPHARMACEUTICALS

Several blood flow tracers are available for the evaluation of myocardial perfusion using PET (Table I). Based on the mode of production, these radiopharmaceuticals are divided into two groups. Rubidium-82 ([^{82}Rb]-) and copper-62 ([^{62}Cu]-) pyru-

TABLE I Extraction Fraction (EF), Tissue and Physical Half-life, and Emitted Positron Energy for Tracers Used for Determination of Myocardial Blood Flow with PET

	PET Myocardial Blood Flow Tracer			
	EF	Tissue Half-life	Physical Half-life	Positron Energy MeV
Generator-produced				
Rubidium-82	~65%	Long (hrs)	1.3 min	3.3
Copper-62	~60%	Long (hrs)	9.8 min	2.9
Cyclotron-produced				
$[^{13}N]NH_3$	~90%	Long (hrs)	10 min	1.2
$[^{15}O]H_2O$	~100%	Short (sec)	2 min	1.72
^{11}C microspheres	~100%	Long (hrs)	20 min	0.96

valdehyde-*bis*-(*N*-4-methylthiosemicarbazone) (PTSM) are generator-produced radiopharmaceuticals; $[^{13}N]NH_3$, $[^{15}O]H_2O$, and ^{11}C-labeled compounds require an on-site cyclotron for their production.

Generator-produced flow tracers: The strontium-82 (^{82}Sr)/^{82}Rb generator-produced flow tracer is commercially available. The radiopharmaceutical ^{82}Rb, recently approved by the U.S. Food and Drug Administration for the evaluation of myocardial blood flow,[4] is currently the most practical tracer available for PET imaging. The $^{82}Sr/^{82}Rb$ generator is being used in combination with a dedicated infusion system, which permits safe and reproducible administration of ^{82}Rb with minimal radiation exposure to the technical staff (Figure 1). The short physical half-life of ^{82}Rb (76 seconds) allows blood flow measurements in short time intervals. By combining the use of ^{82}Rb with pharmacologic stress testing, regional myocardial flow reserve can be evaluated in about 1 hour, which compares very favorably with the time required for the acquisition of thallium-201 (^{201}Tl) or technetium-99m (^{99m}Tc) isonitrile single-photon emission computed tomography (SPECT) stress studies.

The practical advantages of ^{82}Rb are somewhat offset by the physiologic and physical properties of this tracer. The myocardial extraction fraction of ^{82}Rb is lower than that of ^{201}Tl, and it decreases considerably with increasing blood flow. Therefore, high flow rates produce inaccurate measurements due to the nonlinear relationship between ^{82}Rb tissue retention and blood flow. Furthermore, ^{82}Rb emits positrons with an energy of 3.3 MeV that travel a longer distance than those of ^{13}N or ^{11}C in tissue before they annihilate with electrons. Thus, the image resolution obtainable with ^{82}Rb is less than that available with $[^{13}N]NH_3$ (Table I). However, the loss of resolution by the high energy of ^{82}Rb positrons is small in comparison to the effect of cardiac motion on the spatial resolution of nongated cardiac images.

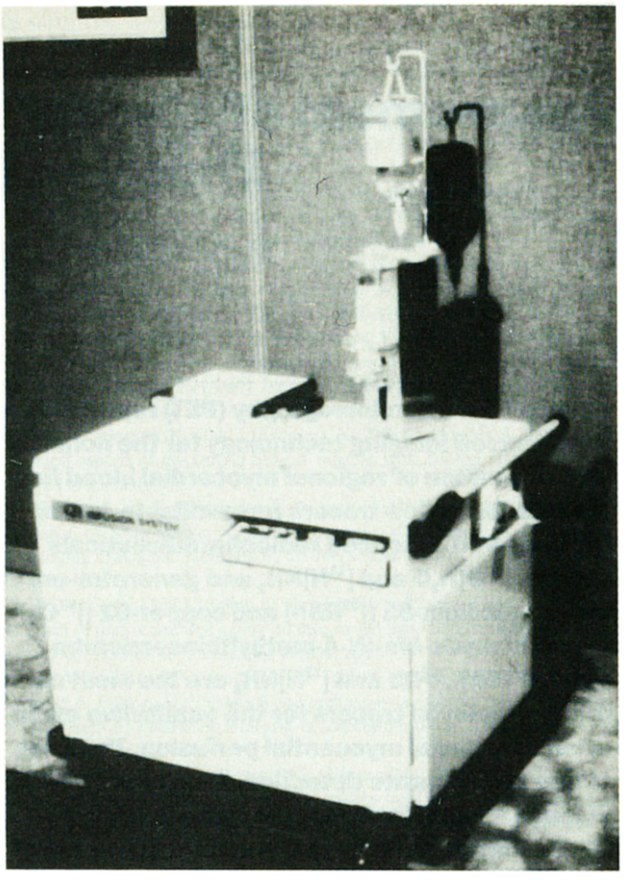

FIGURE 1. $^{82}Sr/^{82}Rb$ generator mounted to a computer controlled infusion system to allow convenient administration of the compound to the patient.

$[^{62}Cu]$PTSM represents a newly introduced flow tracer produced with the zinc-62 (^{62}Zn)/^{62}Cu generator. Although this radiotracer has been validated only in experimental studies, the preliminary results are promising.[5] ^{62}Cu has a physical half-life of 9.8 minutes and, like ^{82}Rb, exhibits a high positron energy (Table I). The myocardial extraction of PTSM is similar to that of ^{82}Rb, and the clearance from myocardial tissue is slow—both desirable characteristics for blood flow imaging. The usable time period for a $^{62}Zn/^{62}Cu$ generator is only about 24 hours, in contrast to the $^{82}Sr/^{82}Rb$ generator, which has a shelf life of about 6 weeks. This may limit its distribution, as well as the availability of a continuous supply of compounds for the evaluation of myocardial blood flow. However, in combination with a centrally located cyclotron, generator-produced flow tracers such as $[^{82}Rb]$- or $[^{62}Cu]$PTSM can be combined with $[^{18}F]$deoxyglucose for the simultaneous evaluation of blood flow and tissue metabolism without the need of an on-site cyclotron.

Cyclotron-produced flow tracers: The cyclotron-produced tracers most commonly used for the evaluation of myocardial blood flow are $[^{13}N]NH_3$

and $[^{15}O]H_2O$. Figure 2 shows the time course of both tracers in myocardial tissue and blood pool, following an intravenous bolus injection. The compound $[^{13}N]NH_3$ has a physical half-life of 10 min, is avidly taken up by the myocardium, and clears rapidly from the blood pool. It enters the extravascular space and is converted in myocardial tissue to $[^{13}N]$glutamine.[6] The clearance half-time of ^{13}N from the myocardium is slow, and yields a high contrast between myocardial and blood activity. The retention of ^{13}N in myocardium represents a combination of delivery (blood flow) and metabolic incorporation. These physiologic and physical properties of $[^{13}N]NH_3$ provide excellent image quality in combination with PET.

In patients with severely impaired left ventricular function or a history of heavy smoking a considerable amount of $[^{13}N]NH_3$ is retained in lung tissue, thus decreasing the heart-to-lung activity ratio. In contrast to ^{82}Rb, $[^{13}N]NH_3$ is avidly taken up by the liver and may, therefore, affect the evaluation of the inferior wall of the left ventricle if the liver is in close proximity to cardiac tissue.

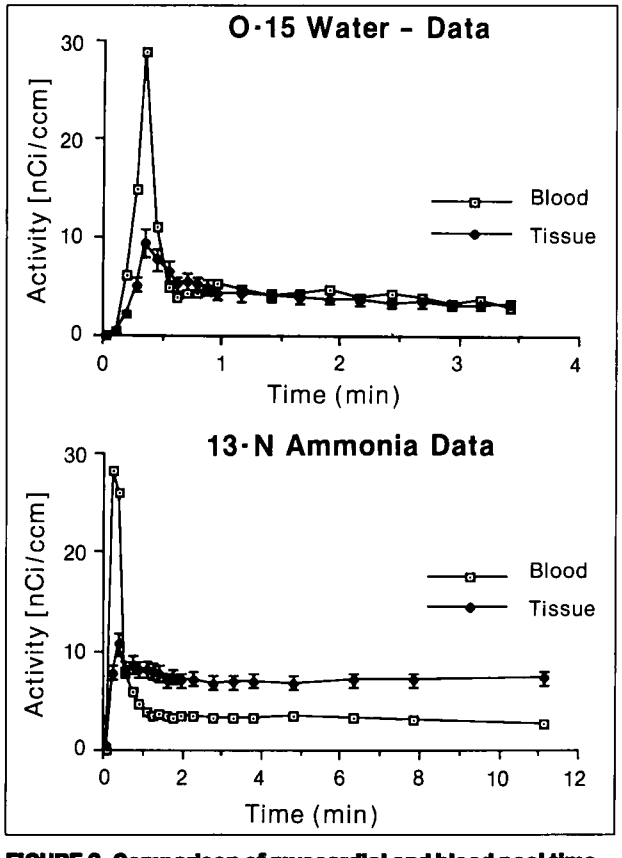

FIGURE 2. Comparison of myocardial and blood pool time-activity curves obtained using $[^{15}O]H_2O$ (above) and $[^{13}N]NH_3$ (below). The arterial input curve (squares) represents blood pool activity and is similar for both tracers. The tissue curve (circles) for $[^{13}N]NH_3$ demonstrates retention of the tracer, yielding high contrast between myocardial and blood activity as early as 1 min after injection. In contrast, the $[^{15}O]H_2O$ tissue activity curve shows little contrast to blood activity due to rapid back diffusion of the tracer from tissue.

The compound $[^{15}O]H_2O$ represents a metabolically inert flow tracer. It diffuses freely across membranes and is highly extracted by myocardial tissue. Animal studies have shown a stable single first-pass extraction of $[^{15}O]H_2O$ over a wide flow range, indicating ideal physiologic characteristics of this tracer.[22] However, $[^{15}O]H_2O$ retained in myocardium diffuses rapidly back into the vascular space. Thus, the contrast between ^{15}O activity in the vascular space and myocardial tissue is small. In fact, the concentration ratio of blood to tissue reaches unity within 60–90 seconds after injection, depending on blood flow (Figure 2). Most studies employing $[^{15}O]H_2O$ for the evaluation of myocardial perfusion are using a separate imaging procedure with $[^{15}O]$carbon monoxide, which labels red blood cells, and thus allows for the delineation of the vascular space within the myocardium and the ventricular chambers. By combining both approaches, the vascular activity can be subtracted and regional myocardial $[^{15}O]H_2O$ retention visualized. This dual tracer approach may limit the clinical application of $[^{15}O]H_2O$ studies because blood pool scans are required under both resting and stress conditions.

Besides $[^{15}O]H_2O$ and $[^{13}N]NH_3$, ^{11}C or gallium-labeled (^{68}Ga) microspheres have been used for the assessment of myocardial perfusion. This tracer approach is limited to the injection of the tracer either into the left atrium or left ventricle, which is only possible in the catheterization laboratory.

QUALITATIVE EVALUATION OF MYOCARDIAL PERFUSION

Qualitative evaluation of regional tracer distribution using ^{82}Rb and ^{13}N has been employed to detect CAD. Taking advantage of the attenuation correction provided by PET, relative tracer concentration is more homogeneous throughout cross-sectional images of normal myocardium, as compared to ^{201}Tl SPECT imaging (Figure 3). Recently published normal data for regional ^{201}Tl retention on SPECT images demonstrate considerable variation between the anterior and inferior walls of the left ventricle in a male population, thus indicating the significant effect of photon attenuation.[7] Attenuation artifacts are common with ^{201}Tl SPECT imaging and may limit the specificity of this test for the diagnosis of CAD.

PET evaluation of myocardial perfusion at rest and during stress provides detection of regional perfusion abnormalities with high diagnostic accuracy (Figure 4). Most stress flow studies are per-

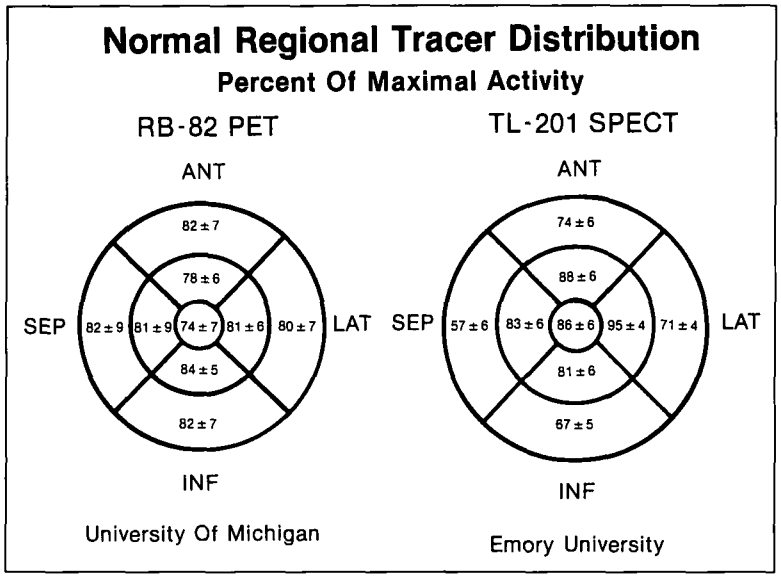

FIGURE 3. Comparison of normal distribution of ^{82}Rb and ^{201}Tl on a polar map display representing regional relative tracer concentration expressed as percent of maximal activity. Data represent average of 15 ^{82}Rb studies (8 male, 7 female) following intravenous dipyridamole infusion. Note the decreased relative ^{201}Tl activity in the inferolateral wall representing soft tissue attenuation. Thallium-201 data adapted from the *Journal of Nuclear Medicine*.[7]

formed following pharmacologic coronary vasodilatation (dipyridamole, adenosine) because the combination of PET with exercise poses technical difficulties, especially if the short-lived tracer ^{82}Rb is employed. Table II depicts recently published diagnostic results using [^{13}N]NH_3 or ^{82}Rb in combination with PET. Schelbert et al[8] demonstrated that use of [^{13}N]NH_3 provides sensitive detection of CAD. Gould et al.[9] employed ^{82}Rb in combination with dipyridamole in a larger group of patients with suspected CAD, and reported a high sensitivity and specificity for the detection of disease. Demer et al.[10] extended this study to 193 patients. The noninvasive assessment of relative coronary reserve by ^{82}Rb PET correlated closely with the angiographic definition of the severity of CAD employing quantitative measurements. These results suggest an excellent diagnostic performance of PET flow imaging for the detection of CAD.

Only a few studies directly compared PET flow imaging with ^{201}Tl SPECT in the same patient population. Tamaki et al.[11] employed [^{13}N]NH_3 PET imaging together with ^{201}Tl SPECT in patients with angiographically proven CAD. Both imaging procedures yielded a high sensitivity for the regional detection of disease. However, this study did not include a normal control population; thus, no conclusions can be drawn about the specificity of both imaging modalities.

More recently, two investigations compared ^{82}Rb PET imaging with ^{201}Tl SPECT imaging in the same patient population. In the first study of 132 patients, Go et al[12] from the Cleveland Clinic reported a significantly higher diagnostic accuracy of ^{82}Rb PET imaging for the detection of CAD. Sensitivity and specificity of ^{82}Rb PET were higher than those of ^{201}Tl SPECT and yielded a significantly improved diagnostic accuracy of 92% for

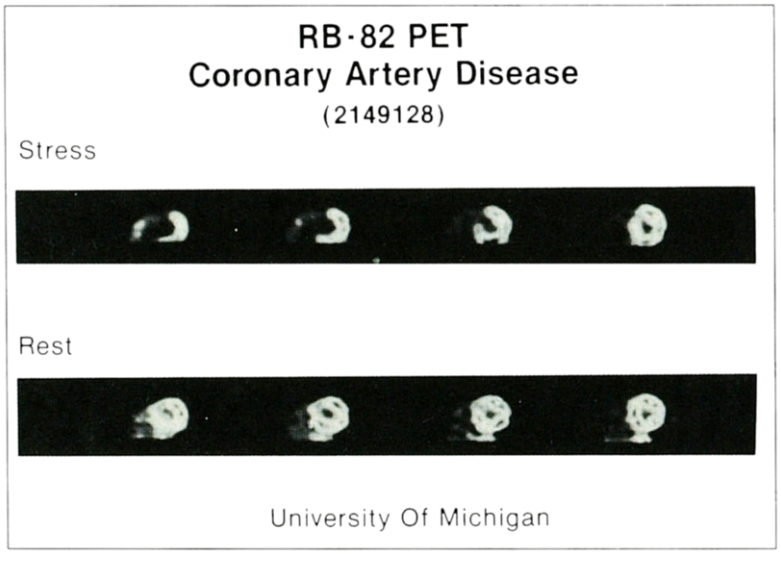

FIGURE 4. Cross-sectional ^{82}Rb images of patient with significant left anterior descending artery (LAD) stenosis. The resting study below shows homogenous myocardial ^{82}Rb activity. Following intravenous dipyridamole infusion, a marked perfusion abnormality is noted in the anteroseptal wall consistent with impaired coronary reserve in the LAD territory. Note the dilatation of left ventricular chamber as indirect evidence of the significance of the dipyridamole-induced perfusion abnormality.

TABLE II Diagnostic Performance of PET and Tl-201 SPECT for Detection of Coronary Artery Disease

First Author	PET						SPECT			
	N	Tracer	Stress	Sen (%)	Spec (%)	Acc (%)	N	Sen (%)	Spec (%)	Acc (%)
Schelbert et al[8] (1982)	32	NH_3	Dip	97	100	98	—	—	—	—
Demer et al[10] (1989)	193	NH_3Rb	Dip	94	95	94	—	—	—	—
Stewart et al[13] (1991)	81	Rb	Dip	85	89	86	81	83	61	77
Go et al[12] (1990)	132	Rb	Dip	95	82	92	135	79	76	78
Tamaki et al[11] (1985)	48	NH_3	Ex	98	—	—	48	96	—	—
N = Number of patients:	492			94	92	93	264	86	69	78

Acc = accuracy; Dip = dipyridamole; Ex = bicycle ergometer; NH_3 = [^{13}N]ammonia; Rb = Rubidium-82; Sen = sensitivity; Spec = specificity.

PET as compared with 76% for SPECT. Both imaging procedures followed a single infusion of dipyridamole, thus avoiding the variability of repeated stress testing in the study population. The results of the second study, performed at the University of Michigan, failed to confirm the higher sensitivity of ^{82}Rb PET for detection of CAD.[13] Both PET and SPECT identified disease correctly in about 85% of the cases. However, PET significantly out-performed SPECT in terms of specificity (Table II). The overall diagnostic accuracy of PET and SPECT agreed closely with the data obtained by Go et al.[12] Although patient selection for cardiac catheterization may explain the low specificity of ^{201}Tl SPECT described by the Michigan study, several recent studies indicate the relatively high incidence of false-positive ^{201}Tl SPECT results.[14,15] ^{82}Rb PET showed a significantly lower rate of false-positive findings in the same patient population. The diagnostic difference was most obvious in the diagnosis of disease involving the inferior wall of the left ventricle. Diaphragmatic attenuation artifacts appear to be less common with ^{82}Rb PET imaging, which clearly indicates the limitations of the low energy tracer ^{201}Tl for SPECT imaging. Future use of ^{99m}Tc-labeled radiopharmaceuticals may overcome some of these limitations, but sophisticated attenuation correction of SPECT images may be required to match the advanced imaging technology provided by PET instrumentation.

Thus, PET in combination with ^{82}Rb or [^{13}N]NH_3 yields higher diagnostic accuracy for detection of CAD as compared to ^{201}Tl SPECT. This primarily reflects the improvement of scintigraphic data acquisition provided by PET. Preliminary studies analyzing the cost of PET imaging and its impact on the management of patients with proven or suspected CAD suggest an overall cost-saving effect due to less unnecessary cardiac catheterization.[16] However, the question remains whether the higher diagnostic accuracy of this modality justifies the increased costs involved with this test. Further investigation will define the economic cost–benefit ratio of PET flow imaging for detection of CAD.

QUANTIFICATION OF MYOCARDIAL BLOOD FLOW BY PET

As outlined above, PET provides the most sophisticated technology to quantify regional tracer concentration in the myocardium. The time course of tracer distribution in myocardium and blood can be defined by using dynamic image acquisition. The most commonly used flow tracers are [^{13}N]NH_3 and [^{15}O]H_2O. In order to quantify myocardial blood flow in units of ml/min/100 g, the accumulation and fate of the radiopharmaceutical in myocardial tissue must be described by appropriate mathematical models. The exchange of tracer between vascular space and tissue is commonly described in terms of compartmental models. These models rely on two basic assumptions: first, the tracer is homogeneously distributed in these compartments; and second, the transfer from compartments occurs with conservation of mass. Theory and application of compartmental analysis require the development of a current model for the behavior of any particular tracer in the biologic system. Knowledge about the physiologic behavior of the tracer should provide justification for the specific structure as well as the parameters of the compartmental model.

The configurations of compartmental models used frequently for quantification of blood flow are shown in Figure 5. The two-compartmental model consists of a vascular as well as an extravascular compartment. It is most applicable to the description of the tracer kinetics of freely diffusable blood flow tracers such as [^{15}O]H_2O. The injected tracer is delivered by the vascular space, diffuses immediately across the membrane, and equilibrates within the tissue. The exchange between the two compartments is expressed by the rate constants K_1 and k_2. In case of freely diffusable tracers, values for blood flow are usually derived from the estimation of k_2, which represents the clearance of activity from tissue.[17]

In contrast, the description of tissue kinetics for [^{13}N]NH_3 requires a more complex three-compartmental model (Figure 5). The vascular compartment represents the tracer concentration in plasma

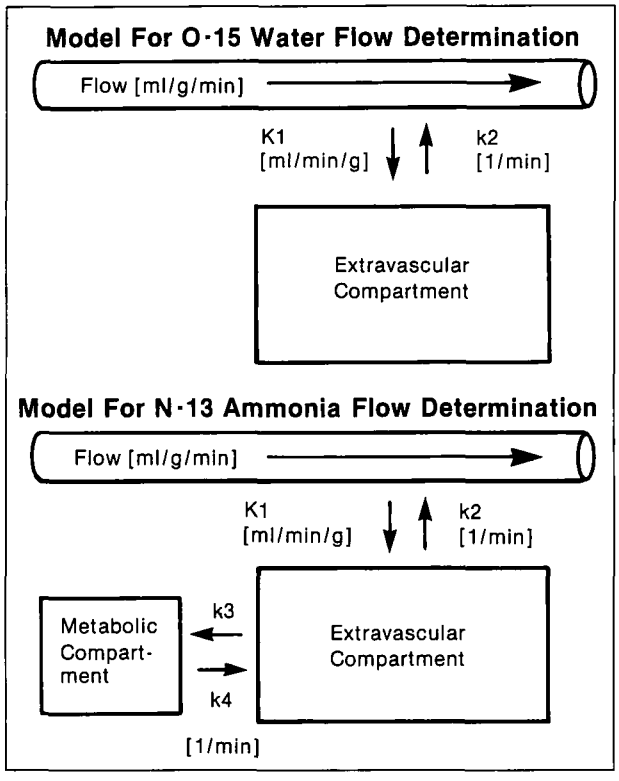

FIGURE 5. Tracer kinetic models employed for determination of blood flow using PET data. The model used for $[^{15}O]H_2O$ (above) is based on the principle of inert gas exchange and can be described by a single tissue, 2-compartmental model.[17] The flow (F) is computed from the washout rate constant k_2 according to the formula $k_2 = F/p$, where p represents the partition coefficient of water between blood and tissue. The myocardial retention of $[^{13}N]NH_3$ depends on its metabolic incorporation into glutamine via the glutamate-glutamine pathway. A 3-compartmental model including the rate constants K_1, $k2$, and k_3 has to be used to separate initial extraction from back-diffusion (k_2) and retention (k_3). K_1 is usually written with a capital letter in order to indicate that it expresses a clearance rate constant rather than a transfer rate constant. The plasma activity concentration has the dimension μmol/ml and the activity concentration in tissue the dimension μmol/g, where K_1 is expressed in ml/min/100 g as an index of myocardial blood flow. The rate constants k_2-k_4 are expressed in min^{-1}.

of the coronary capillaries. The two extravascular compartments represent different chemical states of the tracer but do not distinguish between anatomically separable spaces. Within the extravascular compartment, the tracer competes for back diffusion into the vascular space (k_2) and transfer into the metabolic compartment (k_3). In the case of $[^{13}N]NH_3$, the label is trapped in the myocardium in the form of [^{13}N]glutamine.[18] The release of ^{13}N activity from myocardium is very slow. Therefore, for the description of $[^{13}N]NH_3$ kinetics, k_4 (describing the metabolism of [^{13}N]glutamine) can be neglected in view of the short physical half-life of $[^{13}N]NH_3$ (10 minutes). In this model, the blood flow equals K_1 times the single-pass extraction fraction of the tracer. $[^{13}N]NH_3$ is extracted from blood with a high extraction fraction.[3] Based on experimental data by Schelbert et al.[18] the single-pass extraction fraction only slightly decreases in high-flow states, and is assumed to be greater than 90%, even for flow values up to 500 ml/min/100 g of tissue. However, the net retention of $[^{13}N]NH_3$ in myocardial tissue depends on flow and the metabolic incorporation of $[^{13}N]NH_3$. Because not all of the activity entering the extravascular compartment is metabolized, the assessment of flow based on retained $[^{13}N]NH_3$ activity underestimates myocardial blood flow. This is most apparent during high-flow states where k_3 becomes the rate-limiting step for the incorporation of the label into the metabolic compartment. Thus, to minimize underestimation of high flow states, a tracer kinetic model separating K_1 and k_3 is necessary. Detailed descriptions of the tracer kinetic models employed for $[^{15}O]H_2O$ and $[^{13}N]NH_3$ are provided by Hutchins et al,[3] Iida et al,[19] Krivokapich et al,[20] and Bergmann et al.[2]

COMPARISON OF $[^{13}N]NH_3$ AND $[^{15}O]H_2O$ QUANTITATIVE FLOW MEASUREMENTS:

Both $[^{13}N]NH_3$ and $[^{15}O]H_2O$ have inherent physiologic and physical advantages and disadvantages as imaging agents. $[^{13}N]NH_3$ kinetics in myocardium are more complex than those of $[^{15}O]H_2O$, but the longer physical half-life of $[^{13}N]NH_3$ and retention in myocardial tissue make it a superior imaging agent. On the other hand, $[^{15}O]H_2O$ exhibits almost ideal physiologic properties as a flow tracer. However, its short physical half-life and high activity in the vascular space are challenging for current imaging instrumentation. As a result, different kinetic models must be used for quantification of blood flow based on $[^{13}N]NH_3$ or $[^{15}O]H_2O$ kinetics.

As discussed above, the difference between both tracer kinetic models can be expressed by specific rate constants that describe myocardial blood flow. In the case of $[^{13}N]NH_3$, the rate constant K_1 is used, while the washout rate constant k_2 describes blood flow in the $[^{15}O]H_2O$ model. At different physiologic and pathophysiologic states, K_1-based flow measurements are sensitive to changes of the extraction fraction.[21] Estimates of myocardial blood flow by the $[^{15}O]H_2O$ method reflect k_2 and the partition coefficient of water among plasma, red blood cells, and myocardial tissue, which may also vary under different pathophysiologic conditions.[22] In contrast to the metabolically inert $[^{15}O]H_2O$, $[^{13}N]NH_3$ is rapidly metabolized in the liver following intravenous injection, and ^{13}N-labeled metabolites appear rapidly in

blood.[6] The quantification of regional myocardial blood flow by $[^{13}N]NH_3$ requires the definition of the arterial input function. Recent studies indicate that the effect of ^{13}N metabolites in blood on myocardial blood flow measurements is relatively small, and correction for metabolic contamination may not be necessary.[3]

The major advantage of $[^{15}O]H_2O$ is that blood flow measurements are less affected by partial volume effect. The spatial resolution provided by current PET instrumentation ranges between 6 and 10 mm. In the human heart, the left ventricular wall thickness averages between 10 to 20 mm, depending on the degree of wall thickening during the cardiac cycle. Thus, the recovery of tracer information from the left ventricular wall is influenced by partial volume effect. Undersampling becomes most prominent if the left ventricular wall is thinned, such as in patients with previous myocardial infarction or severe contractile dysfunction.[23] Because flow measurements with $[^{15}O]H_2O$ are based on the washout of activity (relative change of activity), the partial volume effect is less important for the accurate estimate of clearance kinetics. Conversely, $[^{13}N]NH_3$ flow measurements depend on the accurate estimate of the initial uptake of this tracer in the myocardium. These measurements are sensitive to the partial volume effect.[24,25] Thus, in areas of previous myocardial infarction, it is expected that $[^{13}N]NH_3$ blood flow measurements will underestimate the true myocardial blood flow.

Although clearance kinetics are less sensitive to partial volume effects, Monte-Carlo simulations have shown that the coefficient of variation for a washout rate constant is about 3 times higher than the same coefficient for an uptake rate constant. It is obvious that further research is required to define the relative error sensitivity of uptake parameters ($[^{13}N]NH_3$) and washout parameters ($[^{15}O]H_2O$) under various physiologic and pathophysiologic conditions.

It is expected that myocardial blood flow can also be quantified using $[^{82}Rb]$- and $[^{62}Cu]$PTSM. Current research is focusing on the development of a kinetic model for ^{82}Rb. The kinetics of ^{82}Rb resemble those of ^{201}Tl. However, the short half-life of this tracer requires PET instrumentation with high sensitivity and count-rate capabilities for the accurate definition of time-activity curves.

APPLICATION OF QUANTITATIVE FLOW MEASUREMENTS BY PET

Shah et al[26] compared the retention of $[^{13}N]NH_3$ in canine myocardium with blood flow as assessed by radiolabeled microspheres. As expected, a nonlinear relationship between both measurements was observed. This accompanied a significant underestimation of myocardial blood flow based on the retained $[^{13}N]NH_3$ activity at high-flow states (Table III). With the introduction of a tracer kinetic model that corrects for the decreasing retention fraction at high flows, a linear relationship between $[^{13}N]NH_3$ and microspheres blood flow could be demonstrated over a wide flow range.[27]

Bergmann et al.[2] validated $[^{15}O]H_2O$ flow measurements in the canine model. Again, comparing scintigraphic measurements with microspheres blood flow, these investigators demonstrated a linear relationship between both measurements over a flow range from 30 to 500 ml/min/100 g (Table III). The correlation coefficient for both measurements was 0.95, which indicates the accuracy of these measurements in the animal model.

Quantitative measurements of regional myocardial blood flow in human myocardium have been performed with both $[^{13}N]NH_3$ and $[^{15}O]H_2O$. Blood flow measurements at rest and following pharmacologic stress are in close agreement with data previously obtained by coronary sinus catheterization or Doppler flow catheters (Table IV). The relative increase of myocardial blood flow (coronary reserve) in normal volunteers was greater than 4 to 1, which again agrees closely with independent measures of coronary reserve by Doppler catheters and studies performed in the animal model.[1] Quantitative flow measurements during stress (Table IV) indicate that the increase in myocardial blood flow is greater following dipyridamole infusion than following exercise. This may reflect the difficulty of reaching adequate cardiac workload with bicycle exercise during PET imaging.[20]

The noninvasive determination of coronary reserve by pharmacologic means may provide a useful and reproducible parameter for the func-

TABLE III Correlation of PET and Microspheres Flow Measurements in Canine Myocardium

Author	Tracer	Flow Range (ml/min/100 g)	Correlation	
Bellina et al[27] (1990)	$^{13}NH_3$	20–500	$y = -0.18 + 1.08x$	(R = 0.96)
Bergmann et al[2] (1989)	$H_2{}^{15}O$	29–504	$y = 0.00 + 1.06x$	(R = 0.95)
Shah et al[26] (1985)	$^{13}NH_3$	44–200	$y = -36.2 + 1.53x - 0.0027x^2$	(R = 0.94)

TABLE IV Myocardial Blood Flow in Humans Determined by PET with [^{13}N]Ammonia or [^{15}O]Water

Author	Tracer	Rest Flow [ml/min/100 g]	Stress Flow [ml/min/100 g]	Stress/Rest	Stress
Araujo et al[28] (1990)	$H_2{}^{15}O$	88 ± 8	352 ± 112	4.00	Dipyridamole
		93 ± 21*	132 ± 27*	1.42*	
Bergmann et al[2] (1989)	$H_2{}^{15}O$	90 ± 22	355 ± 115	3.94	Dipyridamole
Hutchins et al[3] (1990)	$^{13}NH_3$	88 ± 17	417 ± 112	4.74	Dipyridamole
Krivokapich et al[33] (1989)	$^{13}NH_3$	70 ± 17	135 ± 22	1.93	Bicycle ergometer

*Post-stenotic vascular territories.

tional assessment of severity of CAD. Results by Araujo et al[28] and Walsh et al[29] indicate that the regional coronary reserve is markedly decreased in poststenotic ventricular segments. Walsh et al[29] studied patients undergoing coronary angioplasty prior to and following this procedure. The coronary reserve averaged 1.3 in the stenotic area prior to angioplasty but increased to 3.3, 5 days after revascularization. Thus, quantitative flow measurements may be used following angioplasty for the objective assesment of the intervention results, and also as a predictive parameter for restenosis.

In addition to useful diagnostic and prognostic information in patients with CAD, quantitative flow measurements can also provide an objective assessment of drug therapy. Such measurements can also be applied in cardiac diseases characterized by global changes in blood flow.

Flow measurements based on relative tracer distribution are of limited use in such disease groups. In patients with chest pain and normal coronary arteries, [^{15}O]H_2O blood flow measurements have been shown to identify decreased coronary reserve.[30] Thus, among angina patients, PET may provide a unique diagnostic means to identify those patients with presumably small-vessel CAD.

Quantitative flow measurements have also been employed in patients with cardiac transplants.[31] Few studies have suggested that the coronary reserve is reduced in patients with transplant rejection. This indicates altered coronary hemodynamics, with further studies required to define the diagnostic yield of such measurements in the follow-up of patients with cardiac transplantation.

Although the coronary reserve represents a sophisticated tool to describe the functional state of the coronary vasculature, its magnitude is affected by physiologic processes. For example, elevated blood pressure and heart rate increase resting blood flow and decrease coronary reserve.[32] On the other hand, pharmacologic action of dipyridamole or adenosine may be attenuated in some patients, especially if they take medications known to interact with these drugs. Therefore, the interpretation of flow measurements in patients with various cardiac diseases requires careful consideration of all factors which may affect the magnitude of global and regional coronary reserve.

CONCLUSION

PET provides an advanced imaging technology that allows the accurate definition of regional tracer distribution. This technology, in combination with ^{82}Rb and [^{13}N]NH_3, allows for the sensitive and specific detection of CAD. Several studies indicate the superiority of this approach in comparison to standard ^{201}Tl SPECT imaging. However, further studies are needed to define the cost-benefit ratio of this technology for the management of patients with suspected or proven CAD.

PET represents the most accurate noninvasive means to measure regional blood flow and can be used in combination with pharmacologic stress tests to quantify regional coronary reserve. Tracer kinetic models for [^{13}N]NH_3 and [^{15}O]H_2O provide accurate flow estimates over a wide flow range. Quantitative flow measurements by PET provide a sophisticated tool for research and clinical characterization of patients with CAD. Short-lived radiopharmaceuticals used for PET allow the combined evaluation of flow and other tissue functions such as metabolism, which may prove useful in the assessment of the extent and severity of myocardial disease.

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