Cardiac Positron Emission Tomography

A Report for Health Professionals From the Committee on Advanced Cardiac Imaging and Technology of the Council on Clinical Cardiology, American Heart Association

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This statement of the Committee on Advanced Cardiac Imaging and Technology of the Council on Clinical Cardiology addresses the use of positron emission tomography (PET) as a clinical tool for the diagnosis and management of patients with coronary artery disease. Over the past decade PET technology has evolved to the point that clinical PET studies can be performed safely and efficiently in the evaluation of patients with known or suspected coronary artery disease. Two specific uses of PET in management of coronary artery disease have been proposed: 1) noninvasive detection of coronary artery disease and estimation of its severity and 2) assessment of myocardial viability in patients with coronary artery disease and left ventricular dysfunction. The diagnostic use of PET would apply to a large number of patients, whereas its use to assess myocardial viability would apply to a smaller, more select number of patients.

As of February 1991, the available data that have emerged from the few centers with sufficient experience in cardiac PET indicate that this promising and advanced imaging modality can often provide accurate information in both of these clinical situations. PET allows more sensitive data acquisition than single photon emission computed tomography (SPECT). In addition, coincidence detection provides a means of measuring tissue photon attenuation for subsequent correction of emission data. In clinical practice, such attenuation correction results in improved delineation of regional tracer concentration compared with current SPECT methods. Present-generation whole-body PET scanners provide multislice capabilities (up to 31 tomographic levels simultaneously) with an in-plane spatial resolution of 5–10 mm. In comparison, the resolution of tomographic thallium-201 studies using SPECT is approximately 15–20 mm.

However, PET is an expensive technology that, if widely implemented, could increase overall cardiovascular health care costs. To date, only a few studies, involving small numbers of patients, have directly compared the results of PET with those of readily available, less expensive modalities that may also be used clinically to detect coronary disease, estimate its severity, and determine myocardial viability. Thus, there are limited data that may be used to assess the cost-effectiveness of PET relative to standard, more readily available imaging modalities, particularly in studies in which expertise in both PET and standard single photon imaging are comparable in the same investigators' institution.

Detection and Estimation of Severity of Coronary Artery Disease

Myocardial Perfusion Imaging With Positron Emission Tomography

The diagnosis of coronary artery disease by PET is based on evaluation of regional myocardial blood flow with myocardial perfusion tracers. The most commonly used tracers are rubidium-82, ammonia labeled with nitrogen-13, and water labeled with oxygen-15. $^{82}$Rb (half-life 75 seconds) is generator produced, whereas the use of $[^{13}$N]ammonia (half-life 10 minutes) and $[^{15}$O]water (half-life 2 minutes) require on-site cyclotrons. The short half-lives of these agents allow sequential examinations, such as rest–exercise or rest–dipyridamole studies, within a short time frame that is not possible with standard perfusion imaging using $^{201}$TI. The relation between blood flow and regional uptake of either $^{82}$Rb or $[^{13}$N]ammonia is not linear, and at high flow rates, either agent will underestimate regional blood flow. Thus, the nonlinear responses of $^{82}$Rb and $[^{13}$N]ammonia extraction to increases in blood flow

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limit their use in obtaining quantitative flow measurements to estimate severity of coronary artery stenoses. In addition, attempts to quantify flow with either $^{82}$Rb or $[^{13}]$ammonia are compounded by other factors. $^{82}$Rb is considered a potassium analogue, and myocardial uptake of $^{82}$Rb may reflect active cation transport processes across the sarcolemma as well as blood flow; myocardial incorporation of $[^{13}]$ammonia into radio-labeled amino acids must be accounted for in any mathematical model used to compute flow with $[^{13}]$ammonia. These problems can be circumvented by appropriate modeling of the myocardial extraction of $[^{13}]$ammonia, and animal studies suggest that this may be possible with $^{82}$Rb as well.

In contrast to $[^{13}]$ammonia and $^{82}$Rb, $[^{15}]$Owater is a freely diffusible perfusion tracer, and accurate measurement of absolute myocardial blood flow is possible across a wide range of flow values. Absolute regional myocardial blood flow in humans has been calculated noninvasively, with animal validation studies as the basis. However, cardiac images after injection of $[^{15}]$Owater include the oxygen-15 activity of both the right and left ventricular blood pools as well as myocardial activity; myocardial perfusion images can be obtained only after subtraction of the blood pool activity by another positron agent (such as carbon monoxide labeled with carbon-11 or oxygen-15), which may be difficult in a clinical environment. This subtraction process also results in images of lower resolution than those obtained using either $^{82}$Rb or $[^{13}]$ammonia.

The capacity to determine quantitative regional myocardial blood flow noninvasively is unique to PET. Such estimates could be useful in the clinical setting in assessing the efficacy of angioplasty and detecting diffuse abnormalities of myocardial perfusion reserve, such as those that might occur in left ventricular hypertrophy, in the transplanted heart, or in syndrome X. Although the theoretical and practical limitations of obtaining quantitative blood flow measurements appear to be surmountable, most centers rely on qualitative or only semiquantitative interpretation of $^{82}$Rb or $[^{13}]$ammonia images for diagnosis of coronary artery disease and estimation of its severity (i.e., the hemodynamic significance of a coronary stenosis). Exercise studies with short-lived PET perfusion tracers are difficult, and chest motion during exercise will impair both image quality and attenuation correction, so most studies have used pharmacological vasodilator stress with intravenous dipyridamole or adenosine to assess relative regional myocardial blood flow and flow reserve.

**Diagnosis of Coronary Artery Disease**

Numerous studies, each involving a small number of patients, indicate that perfusion imaging by PET with either $^{82}$Rb or $[^{13}]$ammonia identifies abnormal blood flow reserve in most patients with coronary artery disease, suggesting that PET may be a highly sensitive and specific clinical tool for diagnosis of coronary artery disease. In one of two large published studies, Demer et al. compared qualitative assessment of regional myocardial flow reserve by PET with coronary flow reserve calculated from quantitative coronary arteriography in 193 patients. In this study, either $^{82}$Rb or $[^{13}]$ammonia images were obtained at rest and after the combination of dipyridamole–hand grip stress. The defect score measured by PET was scaled subjectively from 0 (normal) to 5 (severely abnormal). The PET score correlated significantly with the flow reserve data derived from quantitative coronary arteriography for each of 243 coronary stenoses, although the correlation was not very high ($r=0.63$). As might be expected with qualitative estimates of flow reserve, when the most severe defect detected by PET was compared with the flow reserve measured for the most severe stenosis, the correlation was higher ($r=0.77$). Demer et al. did not report the sensitivity and specificity of PET in detecting coronary artery disease in their population. However, analysis of their Figure 3 shows that a PET score of grade 2 or more had a sensitivity of approximately 95% and a specificity of approximately 74% in identifying patients with reduced flow reserve by quantitative angiography (defined as a flow reserve of less than 3). This is consistent with sensitivity and specificity values in this same patient population reported in an earlier abstract (94% and 77%, respectively). When a higher threshold was chosen to define normal flow reserve by quantitative arteriography (flow reserve greater than or equal to 4), a higher specificity (95%) resulted. As with any increase in normal threshold values resulting in increased specificity, it must be anticipated that a higher specificity will be achieved at the expense of a substantial reduction in sensitivity. According to the data in the abstract, the threshold resulting in a specificity of 95% was associated with abnormal results in 125 of 152 patients with coronary artery disease, yielding a sensitivity of 82%.

In the other large investigation, Go et al. studied 202 patients with coronary arteriography and $^{82}$Rb PET, using dipyridamole–hand grip stress. These investigators reported a PET sensitivity of 93% in the detection of coronary artery disease and a specificity of 78%, results quite similar to those of Demer et al. When patients who had undergone previous revascularization procedures were excluded, sensitivity and specificity were 95% and 82%, respectively.

**Reproducibility of Measurements**

Considering the relative flow measurements made with either $^{82}$Rb or $[^{13}]$ammonia PET, it appears that the measurements should be sufficiently reproducible, with little intraobserver and interobserver variability. This has been the case for interobserver variability. In the study by Demer et al. there was agreement between two observers about scoring the defects as detected by PET within two grades in 82% of rest studies and 83% of studies obtained during combined dipyridamole–hand grip stress. The two observers agreed in 89% of patients regarding the presence (grade 2 or higher) or absence (grade less
than 2) of significant perfusion defects detected by PET. Intraobserver variability was not reported. Preliminary data from Mody et al. showed significantly greater interobserver variability between three observers in the qualitative interpretation of $[^{13}]$N ammolia images, with no important intraobserver variability.

**Comparison With $^{201}$TI Scintigraphy**

PET has several theoretical advantages over $^{201}$TI studies in the accurate identification of patients with coronary artery disease: PET provides higher resolution images with intrinsic collimation. The higher energy photons released from positron-emitting tracers and routine attenuation correction procedures overcome photon attenuation problems commonly encountered in $^{201}$TI studies. However, in the first published paper comparing PET perfusion studies with exercise $^{201}$TI scintigraphy in the same patients, the results were remarkably similar. Tamaki et al. studied 51 patients (48 had coronary artery disease) by exercise $^{201}$TI SPECT and PET performed with dipyridamole and $[^{13}]$N ammonia. The sensitivity of $^{201}$TI SPECT (96%) in identifying ischemia in patients with coronary artery disease was similar to that of PET (98%). Specificity in detecting disease could not be addressed because only three patients did not have coronary artery disease. Tamaki and colleagues also investigated the relative abilities of SPECT and PET to identify significant stenoses of individual coronary arteries. Again, the SPECT data (81% sensitivity and 94% specificity) compared favorably with the PET data (88% sensitivity and 90% specificity). Results of the PET studies were not significantly different in any vascular area from those of the SPECT studies.

Investigators at a second institution compared $^{201}$TI SPECT with $^{82}$Rb PET, using a single dipyridamole–hand grip stress for both imaging agents. They found improved diagnostic accuracy with $^{82}$Rb PET, results which stemmed primarily from lower sensitivity in the detection of coronary artery disease with $^{201}$TI SPECT (76%) than with $^{82}$Rb PET (95%). The low sensitivity of $^{201}$TI may be related in part to the timing of dipyridamole administration, because $^{82}$Rb was given at the peak dipyridamole effect, and $^{201}$TI was given at least 6 minutes after the peak effect. It is also noteworthy that more than 75% of the false-negative $^{201}$TI SPECT studies that were correctly diagnosed on the $^{82}$Rb PET studies involved the inferior and posterior wall, a region with greater interpretative errors with $^{201}$TI SPECT because of true or perceived photon attenuation. Although this is a known limitation of $^{201}$TI imaging, the two examples of false-negative $^{201}$TI SPECT studies shown in Figures 4 and 5 of the paper by Go et al. might be interpreted by other observers as $^{201}$TI perfusion defects (i.e., true-positive findings).

Preliminary findings from a third institution revealed similar sensitivities between $^{201}$TI SPECT (using exercise or dipyridamole) and $^{82}$Rb PET (using dipyridamole–hand grip) in identifying coronary artery disease (90% and 87%, respectively) and identifying individual coronary artery stenoses (65% and 64%, respectively). It is important to note that in this study, PET had higher specificity than SPECT both in diagnosis of patients (82% and 57%, respectively) and of individual coronary artery stenosis (92% and 84%, respectively). This could represent evidence of enhanced diagnostic accuracy of PET because of fewer interpretative errors related to photon attenuation. However, the low specificity of the $^{201}$TI SPECT results in this study compared with previous $^{201}$TI SPECT results raises the possibility that patient selection factors, such as a posttest referral bias (using an initial abnormal $^{201}$TI test as the indication for subsequent coronary arteriography and PET), could be operative.

**Summary and Recommendations**

PET imaging with $^{82}$Rb or $[^{13}]$N ammonia provides clinically useful and accurate measures of regional myocardial blood flow for the sensitive and specific detection and localization of coronary artery disease. The diagnostic accuracy of PET is at least equivalent to that of $^{201}$TI scintigraphy, and recent data suggest that PET may provide diagnostic accuracy greater than that of $^{201}$TI SPECT. However, widespread clinical use of PET for this purpose could have profound effects on cardiovascular health care costs. Whether the incremental cost of PET is justified by the possible improvement in diagnostic accuracy has not been established. It is the opinion of the committee that the data are not yet available to demonstrate a clear superiority of PET over other currently accepted, more readily available, and less expensive techniques for the routine diagnosis of coronary artery disease or for determining the functional significance of coronary stenosis in patients with established coronary artery disease. The committee recognizes that PET provides valuable information in certain individual clinical situations, such as patients with equivocal $^{201}$TI SPECT results related to questions of photon attenuation or patients whose physical characteristics are likely to raise issues of photon attenuation. The committee also recognizes that the emerging technetium-99m-based perfusion agents may be superior to $^{201}$TI in the diagnosis of coronary artery disease, are less likely to produce attenuation artifacts, and use standard gamma camera equipment already in place in most nuclear cardiology laboratories.

**Assessment of Myocardial Viability**

Left ventricular dysfunction in patients with coronary artery disease is not always an irreversible process stemming from myocardial necrosis or fibrosis, because regional and global left ventricular function will improve in many patients, at times markedly, after coronary revascularization. Until recently, an accurate assessment of myocardial viability often could be performed only retrospectively, after the patient had undergone revascularization. Pro-
spective detection of viable myocardium by PET in such patients is based on the demonstration of intact metabolic activity in regions of severely underperfused and dysfunctional myocardium.

**Positron Emission Tomography Agents**

**[18F]Fluorodeoxyglucose.** This agent (FDG) has been used as a marker of regional exogenous glucose utilization to detect viable myocardium in such hypoperfused regions. In particular, a pattern of enhanced FDG uptake in regions with reduced perfusion (termed the FDG—blood flow mismatch) indicates ischemic or hibernating myocardium that has shifted its metabolic substrate preference toward glucose and away from fatty acids or lactate.

Maintained or enhanced use of glucose, as estimated by the increased regional uptake of FDG relative to blood flow, has been an accurate clinical marker for distinguishing viable myocardium from myocardial fibrosis. Both Tillisch et al and Tamaki et al studied a small number of patients (17 and 22, respectively) with left ventricular dysfunction who underwent surgical revascularization. In these investigations, preoperative identification of metabolic activity in regions with reduced myocardial blood flow (assessed qualitatively by [13]N-ammonia PET) was associated with improved postoperative function in 78–85% of regions. In contrast, improved regional function after revascularization occurred in only 8–22% of regions in which metabolic activity was not demonstrable before surgery. Thus, evidence of preserved metabolic activity in myocardial regions with reduced blood flow in these two studies had a positive predictive accuracy of 78–85% in identification of viable myocardium and a negative predictive accuracy of 78–92%. Changes in global left ventricular ejection fraction after surgery were reported in only one of these studies. Patients with intact metabolic activity (with normal or increased FDG uptake) in regions with reduced perfusion had a significant improvement in ejection fraction, from a mean of 30% before operation to 45% afterward; in contrast, patients in whom metabolic activity was absent in hypoperfused regions had no change in ejection fraction (30% before and 31% after operation). Although each of these studies included only a small number of patients, a relatively large number of myocardial regions with resting wall motion abnormalities were evaluated (79 and 46, respectively). These studies demonstrated that metabolic imaging with PET is a promising method for identification of viable myocardium in patients with coronary artery disease and left ventricular dysfunction.

Because regional uptake of metabolic tracers such as FDG is sensitive to overall metabolic state, rigid standardization of the metabolic environment is necessary to maximize the amount of diagnostic information obtained by this technique. Application of PET imaging with FDG in patients with diabetes mellitus requires normalization of plasma glucose levels and insulin therapy. However, despite improvement of image quality using this approach, there are no data validating the predictive value of FDG uptake for tissue viability in this patient population.

**[18C]Acetate.** This agent has recently emerged as another promising agent for use in PET studies of myocardial viability. Regional uptake and clearance of [18C]acetate is directly related to regional oxidative metabolism, and quantitative analysis of [18C]acetate kinetics may be used as a noninvasive means of calculating myocardial oxygen consumption and oxidative metabolic reserve. Preliminary studies indicate that preserved oxidative metabolism as estimated by [18C]acetate kinetics in regions of reduced coronary blood flow is a marker of myocardial viability both in chronic coronary artery disease and after acute myocardial infarction.

**82Rb.** Reversible and irreversible ischemic tissue injury may also be determined with 82Rb since uptake and retention of this agent is dependent on both coronary blood flow and cell membrane integrity. In regions of myocardial fibrosis, the diminished uptake of 82Rb reflects a reduction in perfusion that is more severe than in regions of dysfunctional but viable myocardium. In the setting of acute myocardial infarction, uptake of 82Rb occurs if blood flow is restored, but leakage of 82Rb from necrotic tissue follows its initial uptake, resulting in a perfusion defect. In addition to net uptake, the kinetics of this ion leak may be used as an index of myocardial viability. Recent data indicate that such an analysis may provide clinical information comparable to that achieved by PET imaging with FDG in patients with acute myocardial infarction.

**Comparison With 201Tl Scintigraphy**

The ability to define regional metabolic activity (and hence provide metabolic evidence of viable myocardium) by PET is unique. However, as noted above, imaging agents that reflect cation flux, such as 82Rb and 201Tl, may also provide clinically relevant information regarding myocardial viability. Because 201Tl scintigraphy is more readily available than PET and is also less costly, it is important to compare the results of 201Tl imaging with those of metabolic PET imaging in identifying viable myocardium in the same patient population. Four published studies, two by Brunken et al and two by Tamaki et al compared 201Tl scintigraphy with PET examinations in which FDG was the metabolic marker. No comparative studies of 201Tl imaging and [18C]acetate PET have been performed to date. The results of these comparative studies should be viewed in light of the previous experience of standard exercise—redistribution 201Tl imaging in detecting viable compared with scarred myocardium. "Irreversible" 201Tl defects on exercise—redistribution 201Tl studies overestimate the frequency and severity of myocardial fibrosis; between 25% and 50% of patients with apparently irreversible 201Tl defects have normal 201Tl uptake and improved regional left ventricular function after revascularization. Thus,
standard exercise-redistribution $^{201}$Tl imaging appears to result in reduced predictive accuracy in identifying viable myocardium, compared with the results of PET imaging discussed previously.

This has been the case in studies by Brunken et al.\(^4\),\(^9\),\(^40\) and Tamaki et al.\(^41\),\(^42\) which directly compared the results of $^{201}$Tl scintigraphy and PET. Brunken et al.\(^40\) initially compared planar $^{201}$Tl scintigraphy with PET images obtained by FDG and $[^{13}N]$ammonia in 12 patients. Among 36 “irreversible” $^{201}$Tl defects on redistribution images, FDG uptake indicated myocardial viability in 21 (58%). Subsequently, Brunken et al.\(^40\) compared regional FDG uptake patterns with tomographic $^{201}$Tl images, in which corresponding tomographic planes could be compared from PET and SPECT data. In this analysis of 26 patients, 47% of “irreversible” $^{201}$Tl defects were identified as viable, based on FDG uptake. Similar results were obtained in the two studies comparing PET and SPECT reported by Tamaki et al., in which 38%\(^41\) and 42%\(^42\) of regions with “irreversible” $^{201}$Tl defects demonstrated FDG uptake and, hence, viability on the PET studies. These data indicate that metabolic imaging using PET methods is superior to standard exercise-redistribution $^{201}$Tl scintigraphy in detection of viable myocardium in patients with left ventricular dysfunction.

**Limitations of Comparative Studies**

All four of these comparative studies involved small numbers of patients. Brunken et al. reported data in only 12 patients in the initial study using planar $^{201}$Tl imaging techniques\(^4\) and in 26 patients in the later $^{201}$Tl SPECT analysis.\(^40\) Tamaki et al.\(^41\),\(^42\) also studied small numbers of patients (22 and 28, respectively) and it is possible that at least some of the same patients were included in both reports. None of the four studies included an independent standard of viability, such as improvement in wall motion after revascularization. There are two additional issues regarding analysis of the $^{201}$Tl SPECT results in these four studies. First, the severity of the irreversible $^{201}$Tl defects was not considered in comparison with regional FDG activity. The level of relative $^{201}$Tl activity within irreversible defects may reflect tissue viability.\(^44\)-\(^46\) Second, postexercise $^{201}$Tl imaging was used in all four studies and followed by only a single redistribution study 3–4 hours later.

**Late $^{201}$Tl Redistribution Imaging**

It is now well established that late imaging at 8–72 hours will demonstrate substantial $^{201}$Tl redistribution in many defects that appear to be irreversible at 3–4 hours, and that late $^{201}$Tl uptake is consistent with viable myocardium.\(^47\)-\(^49\) Of note, the number of “irreversible” defects at 3–4 hours that subsequently show reversal on late imaging (22–54%) is in some studies similar to the frequency of metabolic activity demonstrated by PET in such apparently irreversible $^{201}$Tl defects. Although there are no published definitive studies comparing the results of PET with those of $^{201}$Tl scintigraphy with late redistribution imaging, preliminary data from Brunken et al.\(^5\) indicate that PET may be superior to 24-hour redistribution $^{201}$Tl SPECT imaging in the identification of viable myocardium; in 14 patients, 16 of 30 “irreversible” $^{201}$Tl defects at 24 hours had evidence of myocardial viability, based on FDG uptake. The magnitude of reduction in $^{201}$Tl activity was not considered.

**$^{201}$Tl Reinjection Techniques**

More recent data indicate that the reinjection of $^{201}$Tl at rest after stress-redistribution imaging may also identify viable myocardium within defects that appear to be irreversible on 3–4-hour redistribution studies.\(^5\) Again, the frequency with which “irreversible” $^{201}$Tl defects on standard redistribution images demonstrate viability after $^{201}$Tl reinjection (31–49%) is similar to that reported with PET and metabolic tracers. Moreover, the ability to predict improvement in regional perfusion and function after revascularization using $^{201}$Tl reinjection\(^5\) is similar to that reported with PET.\(^2\) A recent investigation comparing $^{201}$Tl reinjection techniques and PET imaging with FDG in patients with coronary artery disease and left ventricular dysfunction (mean ejection fraction 27%), in which the magnitude of reduction in $^{201}$Tl activity in “irreversible” $^{201}$Tl defects was assessed before and after reinjection, suggested that $^{201}$Tl scintigraphy may provide information comparable to that provided by PET in identifying viable myocardium in patients with left ventricular dysfunction.\(^4\) This study involved only 16 patients, and the effect of revascularization on regional or global left ventricular function was not investigated. Thus, these data require confirmation by a larger series before definitive conclusions can be drawn. It is noteworthy that preliminary findings from another institution\(^5\) comparing FDG uptake with $^{201}$Tl uptake after reinjection in 14 patients have provided concordant data. Additional preliminary data suggest that $^{201}$Tl injected under resting conditions may also provide important information about myocardial viability in patients with left ventricular dysfunction.\(^5\)

**Summary and Recommendations**

Although the amount of published data is limited, PET appears to provide clinically useful and accurate estimates of myocardial viability in patients with coronary artery disease, regional or global left ventricular dysfunction, and regional hypoperfusion. PET provides a noninvasive means of identifying patients with coronary artery disease and left ventricular dysfunction who, on the basis of metabolic evidence of viability in the myocardial territory to be revascularized, may be candidates for coronary artery bypass surgery or angioplasty. PET also identifies patients (those without metabolic activity) in whom there is little chance for improvement in regional and global left ventricular function after revascularization and in whom the risks of revascularization may therefore not be justified.
The committee recommends that PET be used to assess relative regional metabolic activity with FDG in patients in whom myocardial viability is in question, but only in those patients in whom the identification of viable myocardium is an important clinical issue that will lead to changes in management, such as a decision regarding revascularization. Patients with coronary artery disease and regional or global left ventricular dysfunction are candidates for metabolic imaging with PET, particularly those in whom evidence of regional viability on a 201Tl perfusion study is equivocal.

The committee also recognizes and emphasizes that there are new insights regarding the use of 201Tl scintigraphy, including the use of resting 201Tl injections or exercise studies with 201Tl reinjection and/or late redistribution imaging, that hold promise. Comparative data in small numbers of patients suggest that 201Tl imaging may provide most of the clinically relevant data regarding viable myocardium in patients with left ventricular dysfunction. If this initial experience with 201Tl is confirmed by larger patient series, it may become reasonable, from the perspective of health care cost containment, to recommend that PET studies be performed only if an initial 201Tl study does not provide conclusive results.

The new 99mTc perfusion agents may also be useful in detection of viable myocardium. Firm recommendations about the roles of 201Tl scintigraphy, 99mTc perfusion agents, or PET in identifying viable myocardium must await the results of definitive comparative studies. Implementation of multicenter trials comparing PET with conventional techniques for the definition of tissue viability, using standardized data acquisition and analysis, are recommended for objective assessment of the clinical efficacy of metabolic PET imaging.

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