Position Statement: Clinical Use of Cardiac Positron Emission Tomography

Position Paper of the Cardiovascular Council of the Society of Nuclear Medicine

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Since its inception almost 20 yr ago, positron emission tomography (PET) has matured and has moved from the research laboratory into the clinical environment. Improvements in imaging instrumentation, simplification of image acquisition, processing and analysis as well as streamlining and automation of tracer production and synthesis have facilitated its use for routine diagnostic studies. Development of new tracer technologies have expanded the scope of investigations that are now possible with PET, whereas clinical investigations have demonstrated the utility for detection and characterization of cardiac disease. PET has become accepted at numerous institutions as a clinically relevant diagnostic modality. Current estimates indicate that there are about 60 PET facilities in North America (U.S. and Canada), 45 in Europe, 20 in Japan and 9 in other countries, including three in Australia. PET currently represents the most advanced imaging modality in nuclear medicine, is likely to accelerate the clinical application of tracer kinetic principles to various disease entities and represents a unique and powerful research tool for the study of human physiology and pathophysiology.

TECHNOLOGICAL AND OPERATIONAL ASPECTS OF PET

PET possesses several unique features:

- Quantitative imaging ability, because of appropriate corrections for emission images by measured rather than estimated photon attenuation and the depth-independent spatial resolution.
- Availability of an almost unlimited number of radiopharmaceuticals or "true tracers" labeled with short-lived positron-emitting isotopes, for example, ^{11}C, ^{13}N, ^{15}O, ^{18}F and ^{82}Rb.
- High temporal resolution with sampling rates of several seconds, which permits in vivo measurements of regional functional processes (blood flow, metabolism, receptors) in the human heart.

Static or dynamic transaxial tomographic images of the uptake, retention and clearance of positron-emitting tracers in myocardium are obtained with PET. These transaxial images can be reoriented into short-axis and long-axis sections of the left ventricular myocardium. Static images depict the relative distribution of radiotracers in the myocardium and provide qualitative information on the relative distribution of functional processes in the myocardium. Their spatial distribution throughout the left ventricular myocardium can be displayed in the form of polar maps. Rapid serial image acquisition permits the measurement of the arterial input function of a radiotracer and the myocardial tissue response to it. Use of appropriate and biochemically validated tracer kinetic models allows the noninvasive quantification of regional functional processes such as myocardial blood flow, glucose utilization, oxidative metabolism or fatty acid metabolism. More recently developed tracers offer opportunities for characterizing myocardial tissue hypoxia, adrenergic neurons and adrenergic and cholinergic cardiac receptors.

To take full advantage of the unique capabilities of PET, on-site cyclotrons for in-house production of positron-emitting isotopes and synthesis of positron-emitting radiopharmaceuticals are required. Successful development of dedicated medical cyclotrons together with automated tracer production and synthesis have made PET more convenient; yet the start-up and operational costs remain high. As an alternative, generator-produced radiopharmaceuticals such as ^{82}Rb can be used. They obviate the need for on-site cyclotrons but limit studies with PET to the evaluation of myocardial blood flow and, possibly, myocardial

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viability. A second alternative is the regional production and distribution of positron-emitting isotopes or radiopharmaceuticals to institutions with scanners but without cyclotrons. Tracers available through regional distribution centers are currently limited to ^{18}F-labeled compounds with a near 2-hr physical half-life. Such tracers can be used alone or in conjunction with generator-produced PET flow tracers such as ^{82}Rb or with SPECT flow agents.

CLINICAL USES OF CARDIAC PET

Cardiac PET is clinically used for: (a) detection and characterization of coronary artery disease and (b) identification of myocardial viability.

Detection of Coronary Artery Disease

Results of studies with rest and pharmacologic stress perfusion imaging have been reported in peer reviewed journals in more than 500 subjects. Either the generator-produced ^{82}Rb or the cyclotron-produced ^{13}N-ammonia were employed as tracers of blood flow. Characteristically, myocardial perfusion is initially evaluated at baseline and subsequently during pharmacologically induced myocardial hyperemia. Given the short physical half-life of ^{82}Rb of only 75 sec, a study comprising a set of transmission (photon attenuation) and two sets of emission images can be completed within about 1 hr. Due to the longer physical half-life of ^{13}N-ammonia (9.9 min), more time is required for physical decay of tracer between studies so that a complete rest-stress study with ^{13}N-ammonia requires approximately 1–2 hr.

Both tracers yield comparable diagnostic accuracies. Reported sensitivities for the detection of coronary artery disease range from 87% to 97% and specificities range from 78% to 100% (*1–5*). Appropriate correction for photon attenuation together with the high contrast and spatial resolution of PET account for the high diagnostic performance.

One study in 203 patients, performed with near simultaneous injection of ^{82}Rb and ^{201}Tl, reports similar specificities of 78% and 80% for PET and SPECT. The sensitivity was 93% for PET as compared to only 76% for SPECT (*4*). As ^{82}Rb was injected at 4 min but ^{201}Tl at about 9 min after the dipyridamole infusion, a possible decline of the hyperemic response during the interval period has been invoked as an explanation for the lower sensitivity of ^{201}Tl. However, based on coronary sinus flow measurements, the decline in myocardial blood flow during this interval amounts to only about 10% and thus is unlikely to account fully for the observed difference between the PET and SPECT findings (*6*). A second study, comparing exercise or dipyridamole stress ^{201}Tl SPECT to ^{82}Rb rest and dipyridamole stress PET in 81 patients, reported similar sensitivities for both approaches but a significant gain in specificity with PET from 53% to 88% (*5*). Although patient selection might explain the low specificity of thallium testing in the latter study, such "false-positive" results were not obtained when the same patients were studied with ^{82}Rb. The results of both studies differ from those of an earlier study which employed supine bicycle exercise stress and failed to demonstrate a significant difference between both approaches (*3*). Overall sensitivities were 88% (PET) and 81% (SPECT) and specificities were 90% (PET) and 94% (SPECT).

Identification of Myocardial Viability

Several studies have demonstrated the utility of combined perfusion and glucose utilization (with ^{18}F-deoxyglucose) imaging for identifying viable myocardium or potentially reversible segmental contractile dysfunction (*7–13*). The operational terms "blood flow metabolism match" and "mismatch" refer to concordant reductions in both, blood flow and glucose utilization, or reduced blood flow with preserved or enhanced glucose utilization relative to blood flow. This qualitative tissue characterization assesses average transmural blood flow and glucose utilization because the current image resolution precludes the differentiation between endocardial and epicardial layers. Therefore, the term "mismatch" does not necessarily imply the potential for full recovery of contractile function, as scar tissue and ischemically injured but potentially viable myocardium frequently coexist. Conversely, the term "match" does not imply complete transmural scar tissue formation as normal myocardium may coexist with scar tissue. Rather, it implies that contractile function is unlikely to improve following interventional revascularization (*7*).

Tested against the outcome of regional contractile function after interventional revascularization, a blood flow metabolism mismatch was found to be 68%–95% accurate for predicting a postrevascularization improvement in regional wall motion, whereas a "match" was found to be 75%–100% accurate in predicting that segmental wall motion would not improve (*7–13*). The overall predictive accuracy in these studies, which included a total of 117 patients with 384 dysfunctional segments, averaged 82%. Additionally, some of these studies have suggested that the extent of a mismatch may be of value in predicting the improvement of global left ventricular function after successful revascularization.

Although the above findings pertain primarily to patients with chronic coronary artery disease, blood flow metabolism mismatches have also been reported to occur during the early postinfarction period (*14–17*). Whether these "match" and "mismatch" patterns are as predictive as has been noted in chronic coronary artery disease remains uncertain. In other words, whether blood flow and metabolism patterns in acute infarct patients distinguish between persistent ischemia and completed infarction and thus provide a rationale for interventional revascularization or indicate successful reperfusion has not been fully determined. Thus, further investigations in this area are required.

Alternate approaches for the assessment of myocardial viability are widely available. Recent modifications of the standard ^{201}Tl stress-redistribution protocol in terms of delayed redistribution imaging or imaging after tracer rein-

jection have largely overcome the shortcomings of initial 4-hr redistribution ^{201}Tl scintigraphy and have resulted in a statistically significant enhancement of the diagnostic accuracy with which viable myocardium can be identified and distinguished from scar tissue (*18,19*). Two more recent comparative studies in relatively small patient populations have revealed disparities between the two methods. In the first study, ^{18}F-deoxyglucose uptake was increased relative to blood flow in 52 (63%) of 88 myocardial segments that appeared as fixed defects with thallium reinjection techniques (*20*). However, in a subgroup of segments with severe (greater than 50%) nonredistributing thallium defects, ^{18}F-deoxyglucose was present in 51%; the same percentage of segments revealed increased thallium uptake after thallium reinjection, suggesting that the PET and ^{201}Tl SPECT approaches offered comparable diagnostic accuracies. On the other hand, a second study revealed preserved ^{18}F-deoxyglucose uptake in 7 (25%) of 28 segments showing fixed defects with the thallium reinjection technique (*9*). Furthermore, the enhanced FDG uptake in 25% of segments with a fixed thallium defect after reinjection was shown to be predictive of postrevascularization improvement in regional wall motion.

The available data indicate a gain in accuracy for assessment of myocardial viability with PET. This gain applies especially to patients with poor left ventricular function or end stage coronary artery disease in whom the "positive" signal of enhanced FDG localization on PET can be identified with greater diagnostic confidence than the "negative" signal of depressed ^{201}Tl uptake on SPECT. The ability to perform correction for photon attenuation with PET also represents a major advantage, since regions with "irreversibly" reduced tracer activity on SPECT images could represent either necrotic and/or fibrotic tissue or normal tissue with attenuated activity. It is recognized that protocols for studies with PET aiming at the detection of coronary artery disease as well as for the identification of myocardial viability differ between institutions in terms of dietary study conditions, criteria for matches and mismatches between blood flow and metabolism and for image analysis. Therefore, there is a need for greater standardization of these PET procedures and their analyses.

POTENTIAL FOR CARDIOVASCULAR RESEARCH

Given its unique features and the large number of already existing or potentially available positron-emitting tracers, PET offers new opportunities for exploring and defining cardiovascular physiology and pathophysiology in humans. Continuation of current research efforts as well as development of new quantitative tracer techniques are likely to offer new and clinically relevant insights into human cardiac disease. Several approaches for the quantification of regional blood flow in human myocardium have been introduced (*21–27*). Tracer kinetic models have been developed to correct for the nonlinear relationship of tracer retention and blood flow and for the effects of resolution distortion (partial volume effect; activity spillover). Measurements of blood flow at rest and during pharmacologic vasodilation have been employed for the quantification of myocardial perfusion reserve. Validated experimentally and clinically, both the ^{15}O-water and ^{13}N-ammonia methods are currently employed for characterization of myocardial blood flow in coronary and noncoronary heart disease (*28–32*). The noninvasive quantification of myocardial blood flow is likely to contribute further to defining the hemodynamic significance of coronary artery disease, monitoring the progression or regression of disease and monitoring effects of invasive therapeutic interventions. Such quantitative studies may prove equally useful in the study or management of such noncoronary disease as, for example, left ventricular hypertrophy.

Besides ^{18}F-deoxyglucose (FDG), ^{11}C-acetate has emerged as the metabolic tracer most commonly used in the research laboratory. This tracer assesses TCA-cycle flux and thus provides estimates of myocardial oxygen consumption (*33–35*). Such measurements appear to be useful in assessing tissue viability as shown in patients with acute infarction and chronic coronary artery disease (*13,17*). Larger studies are required to further compare ^{11}C-acetate kinetics and FDG uptake in patients undergoing revascularization in order to define the relative advantages of each approach. In noncoronary heart disease, ^{11}C-acetate may provide measurement of cardiac efficiency and be useful for monitoring therapy. Preliminary data suggest that longitudinal studies with markers of blood flow and metabolism are likely to identify high risk patients and to offer algorithms for stratifying patients to the most appropriate therapeutic management. Additional approaches for the assessment of myocardial viability, such as provided by ^{82}Rb alone or the water technique, need further assessment to define their value in the clinical setting (*36,37*). Equally promising are the potential uses of newly evolving tracers for characterizing cardiac presynaptic and postsynaptic neuronal activity (*38–40*). In addition to offering opportunities for exploring the relationship between neuronal control, substrate metabolism, and its regulation and contractile function and electrical activity, these approaches may prove clinically useful for monitoring and optimizing drug therapy.

CONCLUSIONS AND RECOMMENDATIONS

The Society of Nuclear Medicine acknowledges that currently available data have demonstrated the high diagnostic accuracy of PET for the noninvasive diagnosis of coronary artery disease and for the identification of myocardial viability. It is therefore recommended that both diagnostic approaches of PET be reimbursed by public and private health care insurance carriers.

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